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FROM BIOMARKER TO SURROGATE OUTCOME IN OSTEOARTHRITIS — WHAT ARE THE CHALLENGES?

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There is continued interest in the identification and validation of biomarkers in OA. Such biomarkers have multiple potential uses, including the following: exploration of disease mechanisms and dynamics, identification of molecular targets for treatment, identification of patients at risk for rapid disease progression, monitoring effects of disease-modifying therapy, prediction of clinical responses, and tailoring treatment to biomarker levels. The need for biomarkers is particularly acute in the proof-of-concept stages in the development of disease-modifying OA therapy.

It may be speculated that access to useful biomarkers in OA could also eventually have public health benefits, by improving public awareness of risk and decreasing the number of patients required to be exposed to a new drug during the development stage. Availability of biomarkers could thereby also help speed drug development, allow testing of more alternatives in a shorter time, and help shape the design of future drug trials in this complex disease area.

The interest in OA biomarkers is fueled by the increasing prevalence of OA, due at least in part to aging of the population and the seemingly unstoppable increase in frequency of overweight and obesity in many countries. Further rationale for continued OA biomarker research is increasing awareness of the limitations of plain radiography as a method of monitoring OA outcome.

Despite much research in this area, biomarkers validated as surrogate outcome indicators in OA remain elusive. Where do the major difficulties lie? The following comments summarize some useful definitions and criteria for biomarkers and surrogate markers in OA, and highlight specific difficulties in identifying and validating markers for OA.

A clear definition of terms is important when discussing biomarkers:

- A biomarker is a structural or physical measure or cellular, molecular, or genetic change in a biologic process that can be identified and monitored, with resulting diagnostic or prognostic utility. Biomarkers must be reliably and reproducibly measurable by standardized, published methods, be used in several laboratories, and have undergone validation that they measure the intended process with sufficient specificity.
- A surrogate marker or endpoint, on the other hand, is a measurement or biomarker that serves to substitute for a clinically meaningful outcome or endpoint, as well as to predict the effect of a clinical intervention.
- A clinical endpoint, in contrast, is a characteristic or variable that measures how a patient feels, functions, or survives.

It follows from these definitions that, even in the best of cases, only some OA biomarkers can serve as surrogate endpoints for OA. To be validated as a surrogate endpoint a biomarker must be shown to be a reliable substitute measure for, or be able to predict, a clinically meaningful endpoint[1,2].

A significant challenge in the validation of a surrogate marker is that its measurement may not take into account adverse events, since the metabolic processes associated with an adverse event may not be monitored by the marker. Such adverse events may cancel all or some of the treatment benefit. Further, a surrogate marker may not register all beneficial effects of treatment if they are not in the marker pathway. Although a biomarker may have good face validity as a surrogate outcome, changes in concentration may not reflect the molecular or cellular process in the tissue that it is believed to monitor, leading to erroneous conclusions.

As mentioned, biomarkers may have several different potential uses. A general classification has been proposed on this basis[3]. According to this framework, a natural history marker is defined as a marker of disease severity that reflects underlying pathogenetic mechanisms and predicts clinical outcome independent of treatment. Such biomarkers

(type 0) are identified as being of prognostic significance in longitudinal history studies of the disease. Type 0 markers can be used for baseline stratification in clinical trials or as milestones of progression in the natural history of the disease.

Another stage in marker development is assessment of the influence of treatment on the levels of a promising prognostic (type I) marker. A type I biological activity marker is defined as one that responds to therapy. It would likely be evaluated in early stage clinical trials, with the aim of providing proof-of-concept, i.e., that a new treatment indeed has promising activity related to its suggested mode of action. Possibly, a type I biomarker could be used to help estimate the optimal drug dose.

Finally, a type II marker (or composite of several markers) is one that predicts a favorable clinical outcome and thereby reflects the clinical efficacy of a therapeutic intervention. Such a biomarker would be defined as a surrogate marker of therapeutic efficacy. It is likely, however, that any surrogate marker will explain only part of the clinical efficacy, i.e., the proportion of the treatment effect explained (PTE)[4]. As discussed in Reference 3, a correct interpretation of the PTE requires thorough understanding of the underlying mechanisms of the disease and of the activity of the drug. Only if it is known that the agent operates primarily through its action on the marker and the marker is directly in the causal pathway of the disease can changes in marker levels be interpreted reliably.

Validation of a biomarker for its intended use (type 0, I, or II) should follow a stepwise approach, beginning with the initial hypothesis of pathogenesis. Early studies are usually descriptive and cross-sectional cohort studies of limited size. Subsequent validation stages need to expand significantly in size and to be longitudinal, initially retrospective, and later prospective. For biomarkers of type I or type II, access to an active intervention is clearly required.

For a disease-modifying therapy in OA, it may be argued that a clinically meaningful outcome should combine evidence of joint structure (or joint survival) benefit with more direct patient-relevant benefit relating to pain, function, or joint-related quality of life. This clinical outcome would then serve as the gold standard against which any biomarker aspiring to be defined as a surrogate OA marker (type II) needs to be validated. It would appear important that investigators in the field agree on a standard clinical endpoint for each proposed use of a biomarker or surrogate marker. If a "molecular" biomarker is validated against only a "structural" joint outcome, it may serve to examine the relationship of one biomarker to another, but not against a clinical outcome.

This does not necessarily mean that a biomarker that is not fully validated as a surrogate outcome is not useful. It may indeed be useful, insofar as it may help identify a treatment target, or monitor *in vivo* or *in vitro* specific cellular or molecular process of interest in drug development. Biomarker validation is not an all-or-nothing issue, but a process of gradual strengthening of evidence. In validating a biomarker, studies will likely need to account for interactions generated by the particular joint studied (e.g., knee vs hip), stage of disease, comorbidities and medications, ethnicity, sex, age, body mass, and other factors.

The absence of a drug or treatment with unambiguous disease-modifying activity in OA (however defined) greatly hampers any attempt to validate a type II biomarker for OA. Current biomarker work in OA is therefore largely limited to the search for type 0 and type I biomarkers. Most OA-related work to date has taken the "candidate protein" approach of exploring changes in body fluids (blood, urine, synovial fluid) of concentrations of a protein (or fragment thereof) with a known or suspected function in joint cartilage. While several promising candidate markers have been identified through this process[5], this approach has its limitations.

It may be argued that the search for OA biomarkers needs to be expanded genome-, proteome-, and metabolome-wide and accelerated through greater use of large-scale techniques, such as those used in proteomics and exploration of changes in gene expression in joint tissues and circulating blood cells. Finally, for the advancement of biomarker research using either traditional or newer approaches, access to large repositories of biological specimens that are linked to high quality longitudinal clinical data is critical. Given the slow progression of OA, this may be the limitation that is most difficult to overcome.

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ADVANCES IN RADIOGRAPHIC IMAGING OF PROGRESSION OF HIP AND KNEE OSTEOARTHRITIS

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Measurement of joint space width (JSW) remains the recommended method for the evaluation of therapies intended to prevent or retard the progression of OA[1]. However, it has become apparent that the evaluation of hip or knee joint