

What imaging biomarkers are and how they are used

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A useful starting point in thinking about imaging biomarkers is the 2001 workshop report (Atkinson et al, 2001)¹ in which a biomarker is defined as "*a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*". In contrast, a clinical endpoint is "*a characteristic or variable that reflects how a patient feels, functions, or survives*". A surrogate endpoint is a special class of biomarker that regulatory authorities accept can validly substitute for a clinical endpoint in drug approvals. Most biomarkers are not surrogate endpoints.

- *Examples of clinical endpoints are: survival, and patient-reported outcomes such as pain, or ability to perform activities of daily life.*
- *Examples of biomarkers which can be used as surrogate endpoints are: blood pressure in stroke prevention; Q-T interval in drug safety; time-to-progression in cancer; and plasma glucose in diabetes.*

Four broad technological approaches can provide biomarkers:

- Biofluids (blood, urine etc) yielding e.g. molecular (DNA, protein, metabolite) or cellular measures
- Solid tissue samples yielding e.g. molecular, cellular or histopathologic measures
- Physiologic measurements such as lung function, blood pressure or EEG
- Imaging measures

Imaging biomarkers have the unique benefit that they interrogate the exact disease focus such as an infarct or tumour (unlike biofluids and physiologic measurement, which tend to integrate information from the entire body). Moreover, imaging biomarkers are relatively non-invasive (unlike solid tissue samples), and allow followup (again unlike solid tissue samples), especially where imaging modalities without ionising radiation are employed.

Although the concept of imaging measures as biomarkers is relatively new, imaging biomarkers have in fact been used for many years: consider, for example, tumour size, or joint space width in arthritis. In contrast, many genomic and proteomic approaches, commonly considered to be in the biomarker "mainstream", are actually quite poorly precedented.

¹ Atkinson Jr, A., *et al.* Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework Clinical Pharmacology & Therapeutics (2001) 81, 104-107

We can classify imaging biomarkers in several ways

- Diagnostic/prognostic biomarkers – the imaging biomarker helps predict a patient's ultimate clinical outcome.
 - *Any diagnostic radiology examination which involves objective measurement and evaluation could therefore be thought of as providing a biomarker*
- Monitoring biomarkers – the imaging biomarker helps predict a particular patient's ultimate clinical outcome after a particular drug (or other intervention) has been given.
 - *An example of a monitoring biomarker is regular FDG PET monitoring for tumour recurrence following successful cancer therapy*
- Predictive biomarkers – the imaging biomarker helps predict that a particular drug (or other intervention), if given, will change the clinical outcome in a particular patient. This is often described as personalised medicine.
 - *An example of a predictive biomarker is head CT required prior to thrombolytic therapy in acute stroke: if the imaging biomarker shows haemorrhage, this predicts harm if thrombolysis is given. Thrombolytic drug regulatory approval and labelling mandates use of this imaging biomarker*
- Response biomarkers – the imaging biomarker helps predict that a drug (or other intervention) will change the ultimate clinical outcome in a group of patients. Response biomarkers have been enthusiastically adopted by drug developers seeking an early readout of drug efficacy in clinical trial: regulatory authorities have also been encouraging, although understandably reluctant to approve new drugs on the basis of biomarker data alone, without additional evidence of clinical benefit.

Clinical outcome from drug treatment can be thought of in terms of efficacy (benefit or lack of benefit) or safety (harm or lack of harm). Biomarkers used in connection with a drug (or other intervention) can thus be considered efficacy or safety biomarkers. Sometimes the same biomarker can serve both purposes: for example, in arthritis if the rate of X-ray joint space narrowing is slowed with drug therapy, joint space width could be an efficacy biomarker, while if the rate of X-ray joint space narrowing accelerates with drug therapy, joint space width might be a safety biomarker.

Most biomarkers are not surrogate endpoints and cannot validly substitute for a clinical endpoint in regulatory drug approvals. It is helpful to use the term "evaluation" rather than "validation" to capture the idea that use of data from such a biomarker carries a risk, which has to be managed: the term "validated" in common parlance sometimes seems to imply "risk-free" and should be avoided unless carefully defined. For response biomarker, Qualification² has been described as the process of accumulating evidence to link the

² Wagner, J.A. *et al.* Biomarkers and Surrogate End Points for Fit-for-Purpose Development and Regulatory Evaluation of New Drugs *Clinical Pharmacology & Therapeutics* (2007) 69, 89–95

biomarker with underlying biology (e.g. imaging – histopathology correlation) and to link the biomarker with clinical endpoints (predictivity). Importantly it is a "graded evidentiary process" which depends on intended application.

For response biomarkers the intended application could include

- Change in the biomarker after drug treatment helps the drug developer's project management or scientific decision making, e.g.
 - does the drug reach its target intact (drug metabolism and pharmacokinetics)?
 - *example: ^{19}F MRS of 5-fluorouracil in metastatic colorectal cancer*
 - does the drug modulate its molecular target?
 - *example: ^{13}C MRS of glycolytic flux in diabetes*
 - does the drug elicit a pharmacologic response in its target tissue (sometimes called pharmacodynamic biomarkers)?
 - *example: k^{trans} in solid tumours*
 - does the drug ameliorate or reverse the structural changes in disease
 - *example: cartilage thickness in osteoarthritis*
 - helping select doses, schedule, and perhaps combinations
- Change in the biomarker informs the discussion between the drug developer and the regulatory authority about the design of the phase III programme including doses and safety assessment
 - *example: tumour size*
- Change in the biomarker in Phase III trials supports the regulator's decision to approve the drug where the clinical efficacy data are compelling but less extensive than would otherwise be demanded
 - *example: enhancing plaques in multiple sclerosis*
- Change in the biomarker in Phase III trials supports the regulator's decision to approve the drug in the absence of clinical efficacy data (surrogacy, NDA).
 - *example: time-to-progression in some cancers*
- Lack of change in the biomarker in Phase III trials supports the regulator's decision not to reject the drug on safety grounds (NDA).
 - *example: lack of effect on bone mineral density*
- Regarding a drug that has previously been approved, change in the biomarker in supports the regulator's decision to approve the drug for an additional indication (sNDA).
 - *example: atheroma size in cardiovascular disease prevention*

It is important to note that while a biomarker may be qualified for one of these purposes it may not be qualified for another, and the studies needed to qualify a biomarker for one purposes it may be the studies needed to qualify a biomarker for different another.

Typically, imaging biomarker qualification studies address the following questions

- Does the imaging biomarker measure the biological reality purports to measure? For example is infarct volume measured by MRI the same as infarct volume measured by pathology? Typically, these questions are addressed in animal and human studies of imaging-pathology correlation, and/or comparisons between other imaging modalities
- Is the imaging biomarker reproducible and what is the size and timing of the response to intervention (positive and negative control)? These data are required for sample size calculations: estimation of the response to intervention can also be informed by animal studies, particularly when human data are unavailable.
- Is the methodology standardised, robust, and suitable for use in multiple centres with varying levels of expertise?
- What is the normal range of the imaging biomarker across clinical populations?
- Do changes in the biomarker predict the patient's ultimate clinical outcome?

When each of these questions has been addressed, usually in many different trials using where applicable many different types of intervention, the biomarker may finally be considered for surrogacy.