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Qualification of imaging biomarkers for oncology drug development

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Abstract Although many imaging biomarkers have been described for cancer research, few are sufficiently robust, reliable and well-characterised to be used as routine tools in clinical cancer research. In particular, biomarkers which show that investigational therapies have reduced tumour cell proliferation, or induced necrotic or apoptotic cell death are not commonly used to support decision-making in drug development, even though such pharmacodynamic effects are common goals of many classes of investigational drugs. Moreover we lack well-qualified biomarkers of propensity to metastasise. The qualification and technical validation of imaging biomarkers poses unique challenges not always encountered when validating biospecimen biomarkers. These include standardisation of acquisition and analysis, imaging-pathology correlation, cross-sectional clinical–biomarker correlations and correlation with outcome. Such work is ideally suited to precompetitive research and public–private partnerships, and this has been recognised within the Innovative Medicines Initiative (IMI), a Joint Undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations, which has initiated projects in the areas of drug safety, drug efficacy, knowledge management and training.

1. Biomarkers in oncology drug development

Recent developments and discoveries in cancer biology have substantially increased our understanding of cancer at the molecular and cellular levels. The challenge for drug-developers is not only to translate this knowledge into safe and effective therapies for cancer patients, but to do so in a rapid and cost-effective way.

There is a growing need to modernise the drug development process by incorporating new techniques that can predict the safety and efficacy of new drugs better, quicker and at lower cost. One tool is the use of biomarkers, which are of immense importance in oncology drug development. While the ultimate goal for a drug developer is always to show the benefit of the drug in

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clinical end-points (i.e. how a patient survives, feels and functions), most oncology drug development would be impossible without biomarkers. Following Atkinson et al.,[1] a biomarker is, in contradistinction to a clinical end-point, 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'. Using this inclusive definition of biomarkers, even very well established measurements, such as objective tumour response,[2] are properly described as biomarkers, not clinical end-points. Biomarkers can be used to predict response to specific therapies, predict response regardless of therapy, or to monitor response once a therapy has begun.

The biomarkers available to the drug developer fall into two broad technological categories. Firstly, there are molecular markers, which are obtained by removing a sample from a patient, and detecting an analyte, usually remotely from the patient. Examples of these *biospecimen* biomarkers are genetic, genomic and protein analytes detected e.g. from biofluids or tissue samples. Biomarker technologies in the second category remove no material from the patient, but rather detect and analyse an electromagnetic or acoustic *biosignal* emitted by the patient. This class includes electrophysiological and imaging biomarkers (IBs). IBs have unique benefits, but raise unique scientific, technical and regulatory challenges not always encountered with molecular markers.

Biomarkers are essential also in accelerating the identification and adoption of new therapies, but at present there are many barriers for their use in drug development and clinical practice. The AACR-FDA-NCI Cancer Biomarkers Collaborative consensus focused mainly on biospecimen rather than biosignal/imaging biomarkers, but identified critical areas in their recommendations[3] to advance biomarker development in cancer drug development, including standardisation and harmonisation, collaboration and data sharing, regulations, stakeholder education and communication and science policy, which are equally relevant to imaging. In this report we discuss the opportunity to introduce imaging biomarkers (IBs) which show that investigational therapies have reduced tumour cell proliferation, or induced necrotic or apoptotic cell death, together with qualification and technical validation in the context of imaging, the need for standardisation of acquisition and analysis, imaging-pathology correlation, cross-sectional clinical–biomarker correlations and correlation with outcome.

2. Benefits and challenges of imaging biomarkers

IBs exhibit important attributes not often shared by biospecimen biomarkers, in that they can interrogate a large extent (or even all) of the pathological tissue in the body, and also normal tissues, in a single, relatively non-invasive, examination; they can promptly detect small and early focal responses which may predict subsequent benefit or harm and they can often be followed up frequently. However the use of imaging measurements as biomarkers also raises challenges not commonly encountered using biospecimen biomarkers. With biospecimen biomarkers, a defined analyte is commonly quantitated using an *in vitro* diagnostic device, a process quite separate from collection of the sample from the patient. With imaging, however, the quality and validity of the imaging measurement as a biomarker often depends crucially on the use of a diagnostic imaging device, in the presence of the patient, in a manner for which the device (a) was not designed, (b) has not received regulatory approval and (c) is unfamiliar to the user in the trial site. Moreover, for many IBs, the identification of the 'objectively measured characteristic[1]' with a quantifiable concentration of a specified analyte, may be quite impossible.

As molecular biology is leading to new treatment options with reduced normal tissue toxicity, imaging should have a role in objectively evaluating new treatments. New imaging procedures, however, need to be characterised for their effectiveness under realistic clinical trial conditions to ensure that they can reliably identify the best drug at the optimal dose for the right patient group.

3. Current imaging biomarkers and unmet needs

Imaging (and other) biomarkers can be used to predict prognosis; to personalise, i.e. to predict which treatment is optimal for each patient; to monitor treatment in order to detect when change is necessary and to determine whether drugs, doses and schedules elicit a desired or undesired biological effect in certain patients (Box 1).