

BIOMARKERcenter

FREQUENTLY ASKED QUESTIONS



CONTENT

WHAT CAN I FIND IN *BIOMARKERcenter*?

BIOMARKERcenter covers all key biomarker uses at every stage of drug R&D including, disease risk detection, diagnosis, treatment/safety monitoring, and outcome measurement.

The initial focus of *BIOMARKERcenter* was the major therapy areas of: oncology; cardiovascular disease; diabetes; immunology; respiratory disorders and neurological disorders. Therapy areas are continually being expanded and now cover, pain, infectious disease, musculoskeletal and connective tissue disorders and endocrine disease.

For each therapy area, *BIOMARKERcenter* includes not only well-established biomarkers but also high potential biomarkers as identified by industry and academia experts.

The database covers a variety of types of biomarkers including genomic, proteomic, biochemical and cellular (see the 'DEFINITIONS & ABBREVIATIONS' section of this FAQ document). We will begin adding imaging biomarkers to the database in late 2009.

WHAT IS THE STANDARD OF SELECTION TO INCLUDE A BIOMARKER IN *BIOMARKERcenter*?

There must be reliable scientific evidence in a published source to support a specific use of a biomarker. The minimum content for addition to the database is biomarker name and at least one use. Each use must be associated with a disease, adverse event, underlying disease pathology or a drug target and must have a role (diagnosis, predicting treatment efficacy, etc).

CONDITIONS

WHY DO I SEE INDICATIONS OUTSIDE THE SIX CURRENT THERAPEUTIC AREAS IN THE DATABASE?

Biomarkers are not necessarily exclusive to one therapeutic area. They may be related to biological processes that are involved in many different diseases. When a biomarker is added to the database, information on all uses is added whether or not these fall within the main areas.

SAFETY/TOX

WHAT IS THE STANDARD OF SELECTION TO INCLUDE AN ADVERSE EVENT IN *BIOMARKERcenter*?

A Safety/Tox use is created when there is a direct relationship demonstrated between an adverse event and the treatment received by the patients. For example, glutathione-S-transferase M1 as a biomarker of drug-induced liver toxicity or UGT1A1 as a biomarker for risk of irinotecan-induced neutropenia.

EXPERIMENTAL PATHOLOGY

WHAT IS THE STANDARD OF SELECTION TO INCLUDE A BIOMARKER USE IN THE EXPERIMENTAL PATHOLOGY CATEGORY?

An experimental pathology biomarker use is created for a biomarker that indicates the underlying cause of a condition or a toxic reaction. For example, VEGF as a biomarker of angiogenesis in cancer, HOXB1 as a biomarker of oxidative stress in Alzheimer's Disease or XRCC1 as a biomarker of the DNA damage response pathway in cancer.

WHAT IS THE ROLE OF KEY OPINION LEADERS IN THE SELECTION AND RECOMMENDATION PROCESS?

The key opinion leaders provide guidance on which biomarkers are appropriate for inclusion in the database and details on the uses being studied, as well as suggestions on information sources (for example new congresses — which ones are most worthwhile for content, which ones are more political in nature, etc).

Of course, in addition to this expert guidance, the information sources we use (biomedical literature, scientific congresses, clinical trials information, regulatory information, patents, press releases and other company information) are continuously and proactively monitored by our own scientific staff for new biomarker information.

Thomson Reuters has a long tradition of working with key opinion leaders to support product and content development and this approach has been extended to the area of biomarkers.



WHO ARE THE KEY OPINION LEADERS?

The names of the current key opinion leaders involved in *BIOMARKERcenter* are listed below. Their role is to seed the database, then on a regular basis to identify new biomarkers and/or uses to add to the database. They also provide content and product advice as the database evolves.

Professor Jeffrey S. Ross, M.D.
(Oncology)

Professor Juan Carlos Kaski
(Cardiovascular Science)

Dr Trevor Hansel
(Respiratory Disease)

WHAT ARE THE UPDATE PROCESS AND GUIDELINES?

The database is updated on a daily basis. Our tracking of information sources not only looks for content on biomarkers not yet entered in the database, but also for new or updated information on biomarkers for which there is an existing record. This could be:

- a new use under study (a use is a combination of indication, population, role and technique)
- information indicating that the use has advanced (for example, gone from experimental use to use in humans, akin to a phase change for a drug)
- a relevant new reference to add to the database, albeit one that doesn't prompt a change in a lifecycle status for the biomarker (or information on a new kit in development, as another example).

WHAT IS THE QUALITY ASSURANCE PROCESS FOR DATA ENTERED INTO *BIOMARKERcenter*?

The database is curated by scientists who read the information found in the references, analyze this information and prepare the *BIOMARKERcenter* record, including the information on the biomarker itself and its uses, as well as on the development of any FDA-approved kits associated with a use (depending on the biomarkers lifecycle stage, of course). They are supported by modern, computerized tools to locate literature and patent references and to process the information.

All records must pass through a rigorous quality control process before being released into the database. The quality control team is independent of the editorial team and consists of people educated to at least PhD level. Members of the quality control team, with specific expertise, check individual fields of a record. Then the entire record is checked to ensure all the information is internally consistent.

WHAT ARE THE INFORMATION SOURCES FOR *BIOMARKERcenter*?

Principal information sources are biomedical literature and congresses, clinicaltrials.gov, the FDA website and patent literature (WO, US, EP and JP). Work is underway to expand coverage to include press releases and other information from company websites.

In more detail, the main sources are:

- **Scientific meetings:** Information is taken from meetings that specialize in biomarkers content (such as World Biomarkers Summit) as well as relevant meetings in all therapeutic areas where data related to biomarkers can also be presented (ASCO, ACCR, ADA, AUA, etc)
- **Literature Information:** References are identified by searching MEDLINE® and full-text of peer reviewed journals included in the *Web of Science*. Guidelines from scientific societies are usually included here.
- **Patents:** From four patent authorities: Japan Patent Office (JP), World Intellectual Property Organization (WIPO), US Patents & Trademark Office (US) and European Patent Office (EP).

WHAT ARE THE CRITERIA FOR SHOWING A REFERENCE OR PATENT IN THE "SOURCE" COLUMN OF A *BIOMARKERcenter* RECORD?

If, upon analysis, a document (literature reference, clinical practice guideline or patent document) is found to provide highly relevant information to support a specific use of a biomarker, then the document will be added to the "Source" column.

WHY DOES THE NUMBER OF REFERENCES IN "RELATED INFORMATION" DIFFER FROM THE NUMBER OF REFERENCES IN THE "SOURCE" COLUMN?

As mentioned above, a reference in the "Source" column is directly relevant to a specific use of a biomarker. "Related Information" includes all these source documents as well as other, more general references that are relevant to the biomarker but which do not meet the criteria to be associated with a specific use.

Some of these articles will be linked to new uses established at a later date.

HOW FAR BACK DOES THE INFORMATION GO IN *BIOMARKERcenter*?

When a biomarker is identified in one of the main therapy areas and selected for inclusion in *BIOMARKERcenter*, the editorial analysts search literature from the last five years and clinical guidelines from the previous 10 years.

Due to the fast rate of biomarker research, if a biomarker is relevant, it will be mentioned in papers published during the last five years. Guidelines can be current but not necessarily recently updated, hence the search is expanded to track older (but still current) guidelines.

WHERE DO THE SYNONYMS IN A *BIOMARKERcenter* RECORD COME FROM?

Synonyms are taken from the NCBI, Uniprot, MeSH® terms and Expaty database.

HOW IS A BIOLOGICAL PROCESS TERM ASSIGNED TO A *BIOMARKERcenter* RECORD?

When an editorial analyst finds evidence in a source document to support a link between a biomarker and a particular biological process, the process is indexed.

The most appropriate (usually the most specific but always the most descriptive) term from the Gene Ontology Consortium list is intellectually assigned based on information in the source.

WHAT ARE THE CRITERIA TO LINK A PRODUCT MODIFIER TO A *BIOMARKERcenter* RECORD?

A product modifier (launched drug) is linked to a recommend/approved biomarker when the drug is specifically mentioned in a clinical guideline, or the FDA approval letter states that it is a targeted therapy using a named drug.

The product name may be qualified by the terms "treatment" or "toxicity" in parenthesis. The term "treatment" indicates that the product is named in approval documents that support uses with the role of predicting or monitoring treatment efficacy (e.g. the product trastuzumab in the record for biomarker Her2).

The term "drug-induced toxicity" indicates that the product is named in approval documents that support uses with the role of predicting or monitoring treatment toxicity (e.g. the product irinotecan in the record for biomarker UGT1A1).

What are the criteria to link a mechanism modifier to a *BIOMARKERcenter* record?

A mechanism modifier is linked to a biomarker either:

- a) when the biomarker is a target for a drug or
- b) when the biomarker has a use in predicting or monitoring treatment toxicity. In this case, the mechanism of action of the class of toxic drug is included in the mechanism modifier field and is qualified by the mechanism of toxicity in parenthesis, such as genotoxicity.

WHAT ARE THE CRITERIA FOR INCLUDING DIAGNOSTIC KITS IN *BIOMARKERcenter*?

Kits are included when there is an FDA approval letter.

WHAT ARE THE CRITERIA FOR LINKING AN ORGANIZATION TO A *BIOMARKERcenter* RECORD?

Companies are linked to a biomarker record if they make a kit for which an FDA approval letter has been identified by our editorial analysts.

DEFINITIONS & ABBREVIATIONS

HOW ARE VALIDITIES (LIFECYCLES PHASES) DEFINED IN *BIOMARKERcenter*?

Recommended/approved: Kit or measuring device software is approved by the FDA, and/or the use of the biomarker is described in clinical practice guidelines or consensus development statements have been issued by clinical societies of international standing.

Late studies in humans: The biomarker use has been studied in humans (clinical trials and observational studies) but has not yet been approved by a regulatory authority. Should be studies with over 500 individuals. The objective is to measure efficacy and to establish the relationship found in early studies in humans.

Early Studies in Humans: The biomarker use has been studied in humans (clinical trials and observational studies). Should be studies with less than 500 individuals. The objective of these studies is to measure proof of concept and dose finding.

Experimental: Reports from preclinical studies (laboratory and/or animal studies).

Emerging: First mention of biomarker use, usually from patents and press releases

Discontinued: For a biomarker use that is not "Recommended/approved" for which no data has been reported in 12 months.

HOW ARE VALIDITIES (LIFECYCLES PHASES) ASSIGNED IN *BIOMARKERcenter*?

The highest validity corresponding to each use of a biomarker has to be assigned. This means if a use is reported in papers with results from clinical trials in different phases but the same use is described in a clinical practice guideline, the use will be assigned the validity status "Recommended/approved".

WHAT ARE THE DEFINITIONS FOR ROLES IN *BIOMARKERcenter*?

Diagnosis: The role of this biomarker is to identify or detect a disease.

Disease Profiling: The role of this biomarker is to obtain information about the disease, but there is insufficient data to assign a clinical role. The data is often obtained from high throughput analyses, for example transcript profiling, and might be extrapolated to the processes that cause the disease.

Differential Diagnosis: The role of this biomarker is to distinguish between two or more diseases with similar signs and symptoms.

Monitoring Treatment Efficacy: The role of this biomarker is to identify signs of a change (usually beneficial) as a result of treatment. A biomarker used for monitoring treatment efficacy is usually measured before the treatment starts (baseline) and at stages throughout the treatment (follow up).

Monitoring Treatment Toxicity: The role of this biomarker is to identify signs of adverse effects as a result of treatment. Measured at baseline and at stages throughout treatment.

Prediction of Drug Resistance: The role of this biomarker is to detect possible resistance to a therapy and thus to exclude that therapy from the possible therapies available to the patient.

Predicting Treatment Efficacy: The role of this biomarker is to predict a probable beneficial outcome as a result of treatment.

Predicting Treatment Toxicity: The role of this biomarker is to predict a probable adverse effect as a result of treatment.

Prognosis: The role of this biomarker is to predict the probable outcome of a disease, i.e. how a patient's disease will progress and their chances of recovery. The prediction is based on the usual course of the disease seen in similar patients without therapy.

Monitoring Disease Progress: The role of this biomarker is to monitor the progress of a disease, usually for diseases for which there is no effective therapy.

Risk Stratification: The role of this biomarker is to determine a person's risk of suffering a particular clinical event within a specified period of time.

Risk Factor: The role of this biomarker is to determine a person's risk of a disease on the basis of epidemiological evidence.

Screening: The role of this biomarker is to sort a population into 'healthy' and 'non-healthy'. Screening is an epidemiological process, though the same process may serve for diagnosis as well.

Selection for Therapy: The role of this biomarker is to select a sub-group of patients suitable for a particular therapy.

Staging: The role of this biomarker is to describe how far a disease has progressed in a patient. The stage at diagnosis is often a prognostic indicator of overall survival and can be used as a guide for subsequent therapy.

Toxicity Profiling: The role of this biomarker is to obtain information about the underlying cause of an adverse or toxic event, but there is insufficient data to assign a predictive or monitoring role.

A biomarker use with "toxicity profiling" represents the birth of that use, often the first mention of the association between the biomarker and the adverse event and is always experimental. When new studies that focus on its predictive or monitoring role are added to our database, the role will be changed and upgraded.

WHAT ARE THE DEFINITIONS FOR TYPES IN BIOMARKERcenter?

Anthropomorphic biomarkers: are of the body shape/form, for example body mass index.

Cellular biomarkers: are whole cells, for example cancer cells identified by the Pap test.

Biochemical biomarkers: are chemical entities, for example glucose.

Genomic biomarkers: are variants in the DNA sequence and in the transcription level, for example HER2.

Physiological biomarkers: are body processes, for example systolic blood pressure.

Proteomic biomarkers: are variants in protein sequence, protein levels in a given tissue, proteins interactions, and enzyme activities.

Structural biomarkers: are physical images, for example colorectal tumor margin (image obtained by magnetic resonance imaging, MRI), carotid intima media thickness.

GENERAL

WHO CREATES BIOMARKERcenter?

There is a dedicated team of scientific analysts working exclusively in the biomarkers area. Their educational backgrounds include degrees in medicine, molecular biology and biochemistry. A separate team of PhD-qualified scientists is responsible for quality control. We also benefit from expert input from analysts working in the areas of genes, patents, kits, selection of literature, companies and markets. The full team is around 80 people.

IS THERE AN ALERTING FUNCTION?

Yes — you can save a search and set it up as an alert using Save Query. Alternatively, you can choose "Keep Me Posted" to be alerted to updates for individual BIOMARKERcenter records.

IS IT POSSIBLE TO SEARCH FOR A GENE VARIANT IN BIOMARKERcenter?

Genes are indexed in BIOMARKERcenter using the name of the wild-type or predominant variant. Information on specific genomic variations such as SNPs is displayed in the corresponding use record.

There will also be more detail in the references related to a specific use of interest and by linking to related information in the Genomics Knowledge Area, for example in gene-related studies.

Of course, it is possible to search for a gene variant in the Genomics Knowledge Area and link to related records in BIOMARKERcenter.

IS IT POSSIBLE TO SEARCH ON FREE TEXT?

A search in the description field is a free text search. Other fields use controlled vocabulary, rather than free text, to allow more accurate search and retrieval. It is recommended that users select controlled search terms from the browse Index.

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