The importance of biomarker selection in healthcare

ONTOFORCE

Summary

Importance of biomarker selection in healthcare

Biomarkers have repeatedly demonstrated their value in healthcare product development over the last decades[1]. From early preclinical development to post-marketing studies, biomarkers significantly increase the success rates of clinical evaluations by up to 20%, reducing the main cost per patient and facilitating regulatory approval[2-4]. In addition, they offer considerable potential for improving health outcomes[5]. However, their high value is equalized with time-consuming and expensive identification and validation processes. While the relatively limited number of Food and Drug Administration (FDA)-approved biomarkers might indicate that the usefulness of potential biomarkers in clinical development is a challenge to demonstrate[6].

> In general, a biomarker - also referred to as a surrogate end-point or surrogate marker - reflexes the status or progression of a disease, and changes accurately in response to therapy

This paper provides an overview of the necessity of biomarkers during pharmacological and medical product development, the challenges associated with the identification and selection of relevant biomarkers, and, more importantly, how this intensive process can be simplified when efficiently linking and structuring data from several databases into one search platform.

In general, a biomarker - also referred to as a surrogate endpoint or surrogate marker - reflexes the status or progression of a disease, and changes accurately in response to therapy[4]. Clinical biomarkers are typically easier to measure and less expensive than the actual clinical outcome. The concept of a "biomarker" is a comprehensive one. As such, biomarkers serve an almost uncountable amount of various purposes, including supporting the prevention, diagnosis, prognosis, and monitoring of diseases, optimization of patient screening, assisting in treatment decisions and personalized treatment, promoting interception and treatment of adverse events, identifying cell types and pathophysiological processes, and facilitation of medical product development[4,7]. The development of suitable biomarkers can also contribute to understanding the mechanism of action of a drug, selecting the suitable patients for a clinical trial, monitoring and predicting toxicity issues, and guiding regulatory and drug development decisions[8].

Biological components that can serve as biomarkers can vary from simple physiological process measurements, such as blood pressure or pulse measurements, to highly complex and expensive molecular or histological assessments[9]. Any imaginable biological entity can serve as a biomarker: genes, proteins, peptides, hormones, biological processes, or alterations in cells, tissue, or fluids. With the emergence of improved detection technologies, the discovery of new biomarkers is considerably prompted over the last decades.

The importance of biomarkers in the life science field is extensively recognized, as it is demonstrated that more pharmacological products with biomarker data are approved than those without. As such, phase III clinical trials in the absence of a biomarker have a 28.3% success rate, while trial success is increased up to 46.3% in case a biomarker is incorporated during trial design and patient selection[2]. Indeed, clinical studies in breast cancer, non-small cell lung cancer, and metastatic melanoma that used predictive biomarkers to stratify patient populations and define inclusion criteria, confirmed these increased success rates[10]. On top of this, fewer subjects are needed during clinical evaluations to establish clinical efficacy and safety in the presence of biomarkers[11].

A relevant biomarker is thus essential in the trajectory of healthcare development and optimal patient care. However, the selection and validation of biomarkers encounter many challenges. To date, the FDA approved only about 109 unique protein biomarkers, despite encouraging the use hereof, and even fewer are routinely used in the clinic[6,12,13].

The indispensable role of biomarkers in precision medicine

Precision medicine, also referred to as personalized medicine or targeted therapy, gained proper attention over the last years. It allows clinicians to efficiently and accurately predict the most appropriate course of action and treatment for a patient[14]. In contrast to the general one-drug-fits-all model, precision medicine customizes patient healthcare based on the stratification of patients according to differences in genes, environment, and lifestyle. These subgroups can be identified through specific genetic content or other molecular or cellular analysis. In other words, precision medicine is highly dependent on the adequacy of biomarkers[15].

The initial successes with precision medicine – especially in cancer therapy – formed promising new treatment strategies. For example, the well-described HER-2 targeted therapies, introduced in 1990, are effective in patients with breast cancer and overexpression of HER-2[16]. The favorable outcomes of this personalized therapy led to the screening and evaluation of several other cancers characterized by the overexpression of the HER-2 biomarker. However, there is still a sizeable portion of HER-2 positive cancer patients that do not respond to the targeted therapy despite the presence of the biomarker[17,18]. This is probably the result of molecular pathways not being completely understood, resulting in responses other than what would have been predicted in the first place[15].

These findings indicate the need to identify biomarkers that mark resistant diseases and patient therapy respons[19–21]. Because then it could be predicted which patients can benefit from the targeted therapy alone, who needs combination with chemotherapy, or patients that require an alternative therapy approach[22]. A combination of targeted therapies is evaluated as well, with biomarkers playing the central role in identifying proper treatment targets[9,23].

Challenges associated with the identification of biomarkers

Theoretically, the desired characteristics of a relevant biomarker are relatively easy to define: A biomarker ideally needs to be associated with disease severity and progression, should accurately respond to treatment, be highly reproducible, and should be quantifiable[4]. Depending on the disease area, a number of biomarkers have been identified and some are even commonly used in general practice. Although the theoretical idea of a biomarker is a wonderful concept, the identification and selection of a marker that meets FDA requirements for approval is often a complex and laborious process that can take several years[24,25]. At least for biomarkers outside the panel of generally accepted biomarkers in well-known disease areas[8]. As diseases are commonly further stratified according to genetic background, causes, prognosis or treatment response, it is likely that more specific biomarkers will be needed to support each of these patient populations.

The complexity of human physiology

Human physiology is complex. An essential contributor to that complexity, are genetics[14]. Where several distinct genetic mutations can cause the same disease and similar symptoms, patient populations might not respond comparably. This might result from a different underlying cause or molecular pathway, with associated biomarkers not being equal[14].

Despite the tremendous progress in understanding pathophysiological processes underlying disease progression aside from the genetic component of human physiology, many molecular pathways and their response to therapies are not yet completely understood. A potential biomarkers' working mechanism is often a "black box"[4].

Biomarker information is siloed

Each disease area commonly focuses on biomarkers specific for one disease or group of related disease conditions. Even though various databases for colorectal cancer, breast cancer, post-traumatic stress disorders, tuberculosis, urinary proteins, and infectious diseases – to name a few – are widely available, the biomarker information is restricted to that particular field of interest[26–31]. As a result, data is siloed in disconnected databases in various formats and with different focus points. For example, the focus will lie on biomarkers directly or indirectly related to the gastrointestinal system when looking at gastrointestinal diseases. While in reality, biomarkers associated with molecular pathways that influence the gastric and intestinal well-being could also be correlated to other, less obviously related indications.

Harmonization of biomarker nomenclature

The biomarker nomenclature has been used interchangeably for a long time, which considerably hampered research and validation[1,32,33]. As a result, the FDA-NIH (National Institutes of Health) Joint Leadership Council was established to address the need to harmonize terms[34]. In the spring of 2015, the agencies developed the BEST (Biomarkers, EndpointS, and other Tools) Resource, a glossary that clarifies important definitions and distinctions between biomarkers and clinical assessments and their role in research, clinical practice, medical product development, and in the regulation of products by the FDA.

Biomarker nomenclature synchronisation has been applied in practice in some disease areas to date. For example, a clear categorization has been proposed for osteoarthritis that allows for the description of the current status of particular biomarkers and the differentiation between objectively measured biomarkers and patient-reported outcomes[35–38].

Identification and selection of biomarkers

Ideally, biomarkers should be selected based on their relevance and with a specific purpose in mind. Inappropriate selection of biomarkers can easily be detrimental to promising research. So, what is the best approach for identifying, validating, and selecting biomarkers tailored to your research question? The search for a relevant biomarker is currently associated with a considerable amount of text screening and alignment of unstructured information. One way to get started with this process is by searching databases such as PubMed and Medline using specific keywords. Additional data can be retrieved by assessment of biomarker databases correlated with a specific disease. Such an approach requires listing of retrieved data and structuring according to methodology, study type, population, and purpose of the biomarker use to validate the results and assess their validity for your research[39]. A time-consuming task that needs regular updates to align with the most recent discoveries, as the biomarker field is continuously moving.

One platform linking all information

A keyword search consisting of a disease and the term “biomarker” already provides you with the first idea of biological entities that might be of interest. Yet, it remains a challenge to collect the treasure of available information out there efficiently. A way to speed up the search process and to provide a better overview and insights about biomarkers and their use, is to link all the available information to one particular place.

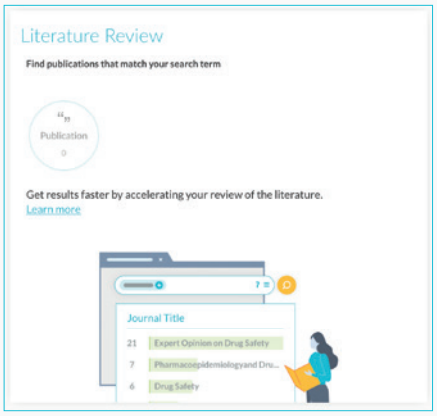
DISQOVER is such a platform where most available life science information from multiple data silos is linked, transformed into a unified format, and structured according to key search terms. Data from different sources can be connected and analyzed quickly through a single point. This allows researchers to swiftly retrieve all publicly available information about a topic, particularly biomarkers of interest, and significantly speed up biomarker selection. Supportive information like associated articles, experts, biomarker type, and eventually available detection methods are displayed in a harmonized format.

Significantly, sources linked by DISQOVER are continuously updated according to the latest scientific findings and can be used by anyone without the need for specific software. This allows users to revise previous searches and amend findings where needed at any point of time.

This is how DISQOVER works

DISQOVER links and structures information from several scientific sources and databases at different levels. For example, a differentiation is made between biomarkers used in clinical studies versus biomarkers described in publications and expert databases. Biomarkers are also subdivided from early research phase to well-validated biomarkers. Furthermore, DISQOVER harmonizes the nomenclature and definition of biomarkers while centralizing and synchronizing the retrieved information. It allows arranging retrieved data to specific interests, such as biological entity, disease area, research institution, etc. Another advantage is linking potential biomarkers with entire molecular pathways, associating disease-related biological components with biomarkers and the relation of the biomarker with downstream pathway molecules. This allows for a broader view and predicting potential interference of the biomarker's direct response to changes in disease conditions.

As a result, DISQOVER is able to support insights in the relevance of biomarkers. A few examples are that it provides an easily accessible overview to explore potential biomarkers in the proper context, differentiates between relevant and undesired information and explores the validation status of biomarkers in specific diseases and disease areas.



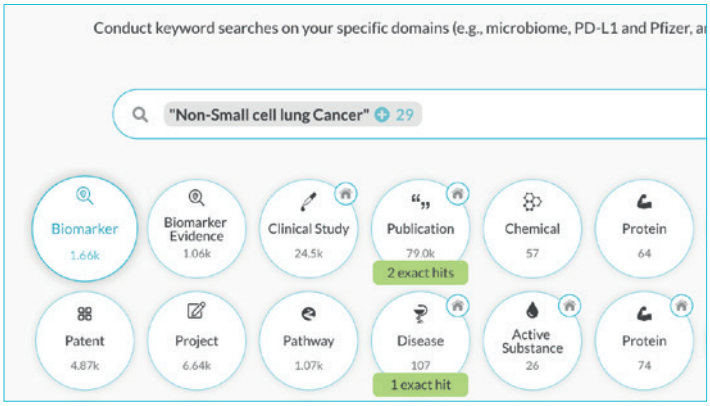
DISQOVER

Conclusion

The added value of biomarkers in life science research and industry is indisputable and highly recognized by the regulatory authorities. They efficiently speed up healthcare development and facilitate regulatory approval. Yet, efforts should be made to make the innumerable amount of biomarker data clear and manageable at an acceptable speed. To do so, siloed biomarker data needs to be linked, harmonized, and structured.

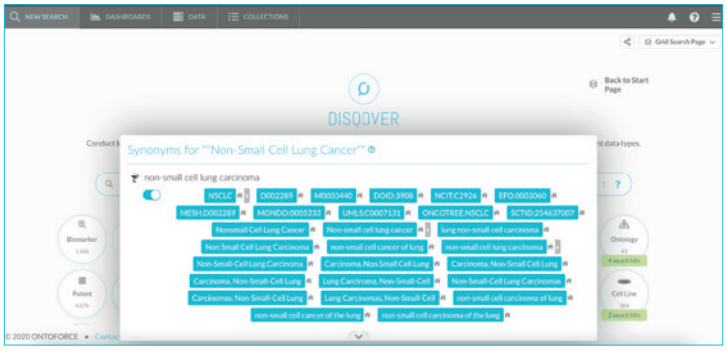
Use cases

Use case 1: Biomarkers associated with Non-Small Cell Lung Cancer



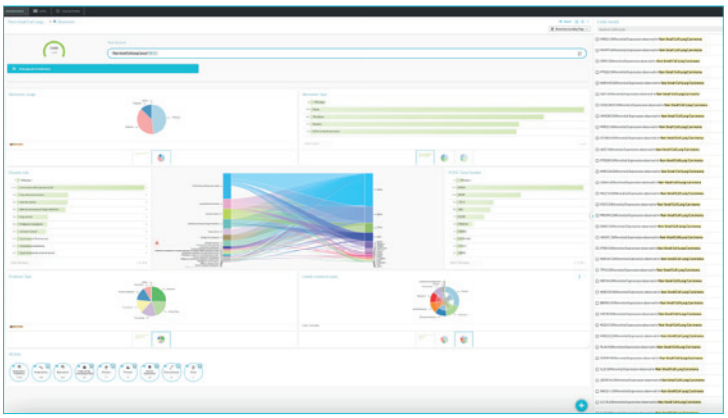
Creating an overview of potential biomarkers of interest related to a specific disease can be a challenge. Because data is siloed, biomarker nomenclature is not entirely aligned, biomarkers are studied in different species or research phases, or the biomarker validity or relevance is unclear.

DISQOVER simultaneously targets these issues. A preview of the platform's added value for the identification, selection and validation of biomarkers can be demonstrated with the following example: Let's say the user wishes for an overview of all biomarkers for which an association is demonstrated with Non-Small Cell Lung Cancer (NSCLC) in the clinical setting. Simply start with adding "NSCLC" into the DISQOVER search field. The user selects the synonyms he want to use. The intelligence of the DISQOVER synonym system disambiguates synonyms for ambiguous search terms. DISQOVER will then provide the user with several areas of interest to which this disease is linked, such as literature, Key Opinion Leaders, and clinical trials. At this point, users can go straight to the 'biomarker' link, showing an overview of biological entities that have been identified and annotated as biomarkers according to the BEST framework in published research articles, databases, clinical trials, or other relevant scientific sources in the NSCLC field[34].



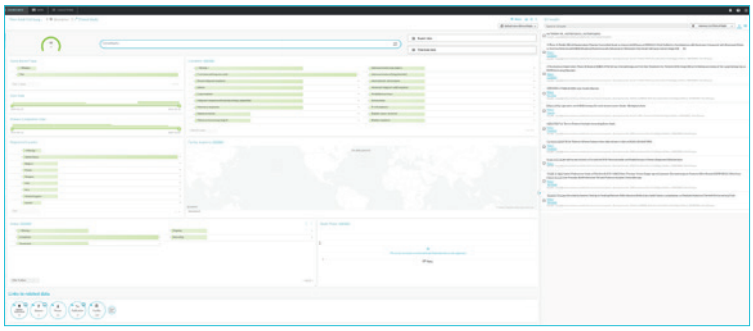
Selection and validation of biomarkers

From now on, the biomarker selection procedure can start. For specific requirements, such as using the biomarker in a clinical setting as intended in the current example, the link selection button "clinical trials" can be checked. The resulting overview will focus only on biomarkers used in clinical research.



The list of potential eligible biomarkers can now be further evaluated. This can be done in several ways and depends on the goal of the original question: Is the user interested in a reliable, well-validated biomarker, or rather in the detection techniques of biomarkers to make sure that biomarker evaluations can be locally performed during a clinical trial? This information can be easily retrieved from the DISQOVER dashboard by looking for example into:

Biomarker validity



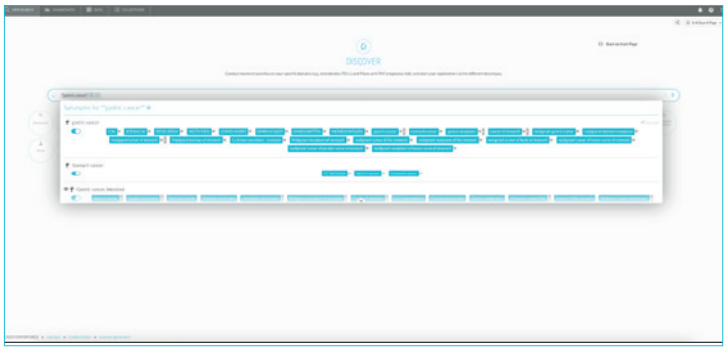
- Different research groups have described a specific biomarker. The more extensive a biomarker has been studied and used, the greater the chances are that the biomarker is accepted in the research field as a reliable factor.
- More details can be obtained for every clinical trial in that list, such as study duration, location, and whether the study is being initiated, ongoing, or completed. Digging deeper into individual studies can be done through the links that DISQOVER shares, connecting users to the source files.

Detection approaches

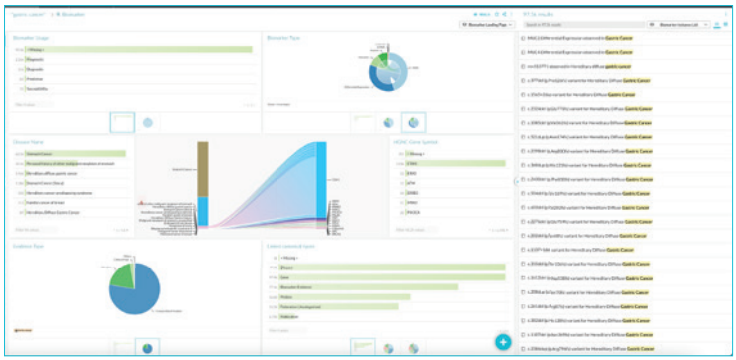
- Information on the type of biomarker, including gene, protein, cell type, etc.
- Selection of a biomarker on the list will provide an overview of relevant information regarding the selected biomarker, including its biological entity, the number and type of clinical trials the biomarker has been used in, and so on. In other words, DISQOVER provides the opportunity to retrieve in a fast way a screening of potential biomarker candidates, tailor-made to specific user requirements.

Use case 2: Identification of Key Opinion Leaders in gastric cancer research

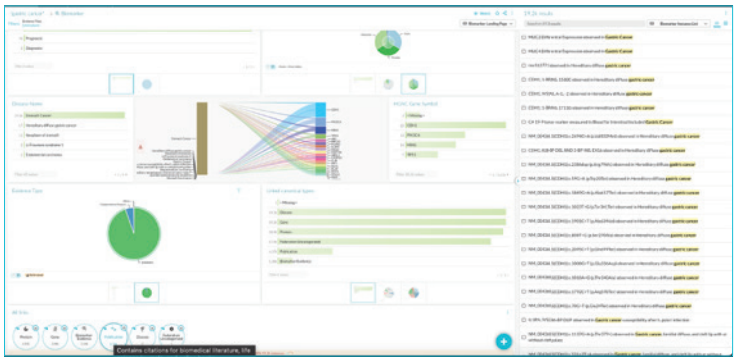
An important aspect in healthcare research and development is the engagement with experts in the field, better known as Key Opinion Leaders (KOLs). They have the best understanding of the latest research and current clinical practice standards. Through the DISQOVER platform, KOLs related to biomarker research can be easily identified. This can be illustrated by the example below showing the tracing of KOLs involved in gastric cancer biomarker research.



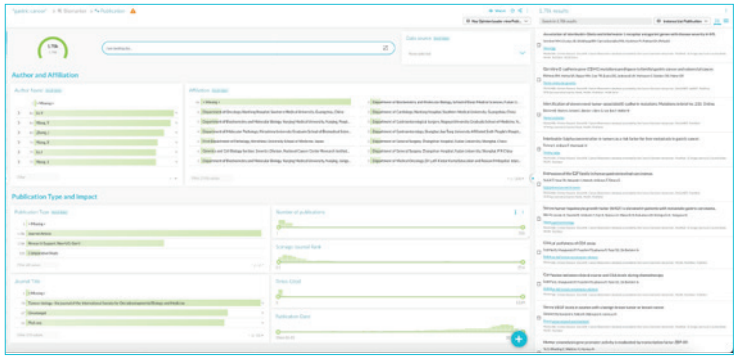
Since gastric cancer is the area of interest, this key term should be inserted first in the search field of DISQOVER. From the list of suggested canonical types, 'biomarkers' can be selected, directing users to the list of biomarkers correlated with this disease and all relationships for this list. Among these relations, the 'Publications' link is the one of interest for this search. Once selected, DISQOVER retrieves a list of all scientific publications associated with gastric cancer and biomarkers. The 'screen for authors' or 'Key Opinion Leader' view will focus on the authors of those publications, or in other words, possible KOLs of interest.



Selection and validation of KOLs



KOLs can be evaluated based on various criteria, some of which are (visually) presented in the dashboard by the DISQOVER platform. These can give researchers a head start on the selection of potential KOLs from the – often – extensive initial list. Basic information, including full names and affiliations from the authors of all the retrieved publications, is presented. Insights into the extent of which each author is involved in biomarker research on gastric cancer can be obtained through the assessment of the provided information, for example:

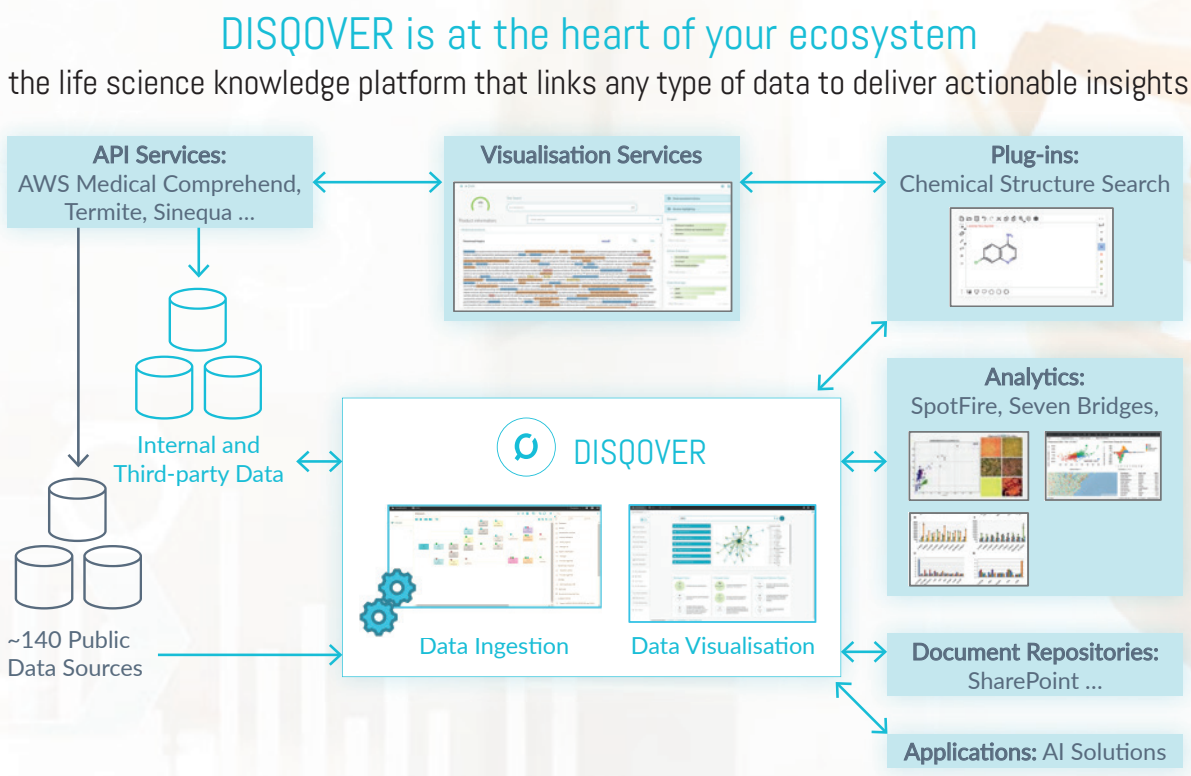


- The number of times a specific author contributed to publications, which gives an idea of the level of involvement of authors in specific biomarker research
- The types of publications that authors are involved in include review articles, original research, case reports, etc. And besides the journal titles, also an evaluation based on impact factor and journal ranking can be performed using the DISQOVER platform
- Selection of a specific author from the list provides an overview of the affiliations and specifications of the journals the selected author is associated with.

As such, eligible KOLs can be selected based on their knowledge and experience of specific biomarker research in gastric cancer.

Use case 3: Public or commercial data?

DISQOVER is a platform that connects and structures related scientific information from separate databases. In addition, the platform is designed so that search results can be evaluated depending on the type of information that is required. For example, results can be evaluated based on biomarker type, specific disease area, experts in biomarker fields, etc. The integrated source data used by DISQOVER can vary, and can be tailored to individual needs.
Primarily, DISQOVER uses about 147 publicly available databases to retrieve information from. These include, for example, PubMed, ClinicalTrials.gov, Reactome, and Orphanet. Next to these freely available databases, commercially available databases can also be connected to the platform. An example is Clarivate, a third party collaborating with DISQOVER. Databases from Clarivate can be linked to DISQOVER, adding their biomarker data to the publicly available sources. This additional data can thus also be scanned, linked, structured, and mapped to the set of data sources standard available. Also, company databases can be added to the platform, making it possible to include individual research data and findings into assessments. As a result, DISQOVER can personalize the platform entirely and can select databases to be included or excluded in analyses. That way, searches can be targeted more precisely and focus on specific research areas or diseases of interest.



Imagine, for example, when a new treatment is approved and marketed in a similar research field as the user's field. The user would like to explore if his research findings can be of interest to repurpose this new drug. Individual research findings, such as preclinical or clinical data demonstrating upregulation or downregulation of specific components, can be compared or fit in public domain information or third-party databases related to that new treatment. This way, own data can provide additional insights into pathways and biomarkers associated with the new drug. They may even open the door to the development of similar acting drugs, perhaps in other indications.
And last but not least, the fact that DISQOVER can be used independently without the need for specific software makes this a suitable tool for self-service that can be regularly updated, rather than providing a one-time report.

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ONTOFORCE TRANSFORMS DATA INTO KNOWLEDGE

For more than a decade, ONTOFORCE has addressed the problem that many Life Science companies struggle with: bringing together structured and unstructured data to create new insights. These insights lead to accelerated drug discovery, more in-depth insights into real-world evidence, optimized clinical trial research and faster go-to-market.

Do you wish to operate analytically, exploratively, or collaboratively? DISQOVER, the knowledge platform of ONTOFORCE, provides these insights quickly, clearly and efficiently. Combine internal data or commercial data with the public data sources of DISQOVER, and you take the lead.

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