Clarivate™

Prioritize indications at scale

An introduction to a systematic approach

Contents

A landscape of increasingly segmented diseases

Innovation in genomic technologies over the past few decades has ushered in an explosion of new drug targets for drug discovery. And while new opportunities abound in this larger target landscape, another important trend is unfolding. The human phenotype dimension is rapidly expanding to reveal a constantly evolving view of a more diverse phenotypic landscape. This landscape is made up of increasingly segmented diseases as we gain more knowledge about the molecular associations with clinical symptoms. A good example is blood cancers. According to the NCI's Surveillance, Epidemiology and End Results Program, what was classified as a "disease of the blood" 60 years ago is 90x more specific today, now being classified as over 40 different leukemia types and more than 50 unique lymphoma types.[1]

Clinical diagnoses have advanced

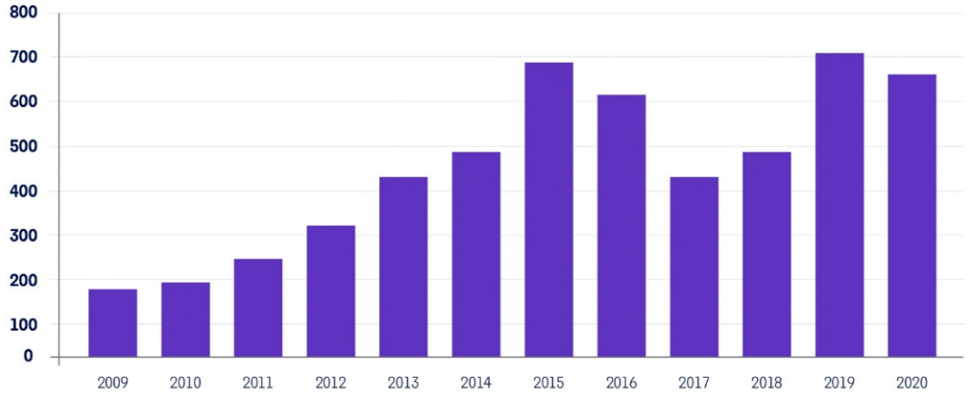
Contributing to this growing complexity in the disease landscape are advances made in clinical diagnostics. Clinical science has progressed to exploit this greater genomic and molecular diagnostic capability, discovering and using biomarkers to stratify patients in clinical trials more effectively. In addition, as artificial intelligence and machine learning techniques continue to develop, patient stratification is being applied more often to better understand the molecular basis of the increasingly narrower patient segments.

Coding has dramatically expanded

Scientists and clinicians have harnessed the increasing understanding of the molecular basis of disease in several ways:

- The headings and disease terms within MeSH (Medical Subject Headings), which is used to index clinical study types from the biomedical literature, are continuously reviewed and updated to reflect greater disease understanding.
- The International Statistical Classification of Diseases and Related Health Problems (ICD) has evolved over time to support more detailed recording and reporting. ICD-11, in effect January 1, 2022, was developed to ensure diseases, and causes for diseases, can be captured more effectively.
- The number of investigational drugs entering the discovery phase in Cortellis Competitive Intelligence™ with a new indication not previously recorded in Cortellis has increased over the past decade (Figure 1).

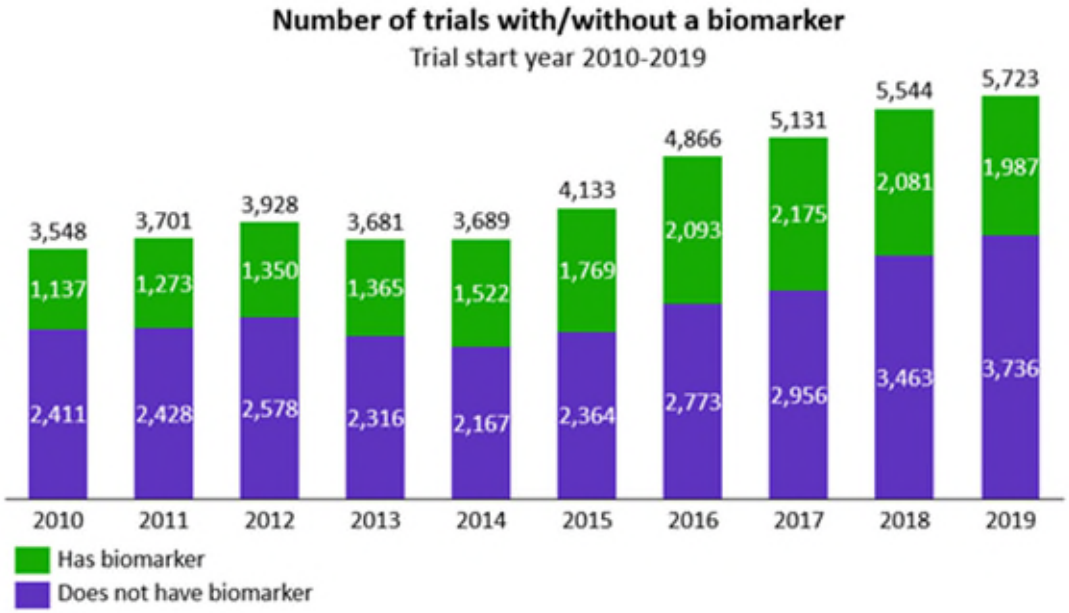
Figure 1. Number of drugs entering the discovery phase the first time for a new indication (three-year moving average)



Source: Cortellis Competitive Intelligence

- Biomarkers are increasingly used in clinical trials to select patients who are more likely to respond to the drug under investigation. Biomarkers are also used as surrogates for clinical endpoints or toxicity effects as well as patient stratification. In oncology, the therapeutic area with the greatest use of biomarkers,[2] the use of biomarkers in clinical trials has increased over the last decade (Figure 2).

Figure 2. Trends in the use of biomarkers in oncology clinical trials



Source: Cortellis Clinical Trials Intelligence™

Risk of repeating a "shots on goal" research strategy

The take-home message is clear: The complexity in both the target (molecular) and patient (phenotypic) dimensions of drug discovery and development has grown quickly in the last two decades, presenting enormous opportunity for pharmaceutical and biotech companies. And while new indications are making their way into discovery programs at an accelerated pace, still only 13% of investigational drugs tested in first human dose studies survive to market launch.[3]

While it is appealing to enter into this new expanding space of target and indication segmentation, it is important not to repeat the narrow view of increasing the "shots on goal" research strategy of the 1990s, which drove R&D spending higher and led to a decreasing return on drug R&D investment,[2] down from 7.2% in 2014 to 1.6% in 2019, but with a slight uptick to 2.5% in 2020, the first increase since 2014.[4]

More effective and efficient methods are required to evaluate this expanding indication space so more meaningful indications can be selected, resulting in more candidates likely to survive clinical development and generate meaningful financial returns.

Methods to prioritize indications

Three major methods currently being used for indication prioritization

Through an analysis of the literature and qualitative assessment of the techniques being used by pharmaceutical and biotech R&D for indication prioritization, those decisions appear to be relying on three major methods, used either individually or in combination:

1. Classical, experimental model

In this model, a compound is tested, and evidence is confirmed in increasingly relevant models of human disease (from in vitro cellular assays to animal models to human outcomes). While this is still the gold standard model from an evidence perspective, the process is costly and slow, and the number of indications that can be studied is small. Equally problematic, animal models have not proven to be reliable models of human disease, the fundamental biological hypotheses are subject to bias and the use of a variety of experimental methods across the drug discovery process can yield confounding outcomes for decision-making.

2. Computational science approach

With this approach, systems biology methods used by bioinformatics analysts evaluate both the association and mechanistic relationship between biological pathways and disease. While this approach is fast and can cover large biological pathway space, the findings are reliant on our existing knowledgebase and may be dependent on experimental validation in either animal models or human trials.

3. Standard management consulting approach

With this approach, a select few indications are profiled based on the assumption that a drug has a role in a small number of chosen indications, and those chosen indications are then analyzed against certain development and commercial criteria, evaluating the market sizing and the clinical and/or regulatory risks. This approach is useful for narrowing options and risk, typically applied later in the R&D cycle; however, its small scale and lack of molecular mechanistic knowledge limit its utility for exploration tasks.

A summary of the three methods is provided in Table 1.

Table 1. Methods for indication prioritization

	Experimental models	Systems biology (computational)	R&D feasibility and commercial (management consulting)
Strength	Accepted standard for evidence	Fast, unbiased, large disease coverage	Narrow options based on known R&D and market constraints and/or risks
Weakness	Subject to biological hypothesis bias, not reliably predictive of human disease, small disease coverage	Connection to human outcomes requires validation	No mechanistic or biological basis of disease, relies on mechanism of action assumptions
Trending	Applied more as validation, not solely explanation	Systematic implementation for exploration	Combined with computational approaches earlier in R&D cycle

Multidisciplinary and pan-R&D process for indication prioritization

At Clarivate, our staff of industry veterans and data science experts have worked extensively in all phases of drug development, from preclinical to commercial forecasting and market sizing domains with both large pharma and smaller biotech.

Our data and expertise

At Clarivate, our vision is to improve the way the world creates, protects and advances innovation. We can better understand the changing drug development landscape by leveraging our deep market expertise, data and insights solutions.

Cortellis Competitive Intelligence™ provides access to data such as drug pipeline, deals, patents, global conferences and company content, along with the latest industry news and press releases.

Cortellis Drug Discovery Intelligence™ focuses exclusively on pharma and drug development, harmonizing and integrating essential biological, chemical and pharmacological data from disparate sources into a single platform.

MetaBase™, a Cortellis solution, delivers high-quality biological systems content in the context of comprehensive, validated biological pathways, giving you essential data and analytics to avoid failed drug development and accelerate your scientific research.

In addition to these specific solutions, Clarivate harmonizes billions of datapoints from thousands of sources and provides a unified view to drive decision-making for a variety of use cases. Specialized consultants and analytics experts help clients turn insights into action and stay ahead of competitors.

Together, we developed an indication prioritization methodology leveraging high-quality content from our products such as Cortellis Drug Discovery Intelligence and MetaBase, a Cortellis solution, in conjunction with advanced analytics from the Clarivate-led consortium **Computational Biology for Drug Discovery (CBDD)**. This methodology brings together the computational and evidence-based approaches of methods two and three, employing efficient, multi-disciplinary metrics that are critical to making good indication prioritization decisions and coupling them more cost effectively with the experimental models of method one.

This approach benefits from operating at a large scale, using evidence-based, manually curated data across many segments of the life sciences, together with mathematical algorithms to inform indication prioritization.

Previous attempts at conducting indication prioritization have concentrated on using only a few methods and disciplines. However, this approach integrates chemical, biological, clinical, regulatory and commercial measures into a multidisciplinary and pan-R&D process that can operate at scale, capable of screening compounds against thousands of diseases simultaneously.

This methodology can operate both in exploratory mode (using drug-to-target combinations together with biological networks and their mechanistic relationship with disease) and in a filtering mode (narrowing indications based on clinical success rates, R&D predicted timelines, regulatory pathways and approvals, incidence and prevalence of patient segments and predicted commercial outcomes based on risk-adjusted, financial return metrics).

Evidence-based approaches for target and indication prioritization

For large pharma, these include profiling compounds under investigation as well as re-examining historical compound collections, quickly, at scale. By using a consistent method to identify candidates for new indications from large compound libraries, scientists and portfolio teams can quickly identify candidates for further investigation.

Biotech companies can start with a single compound. The extensive collections of biological pathways and investigational drugs with their biological properties can be used to explore new indications faster and cheaper than experimental models and can then be quickly filtered based on development feasibility and commercial metrics.

Both approaches produce prioritized indications across thousands of diseases with detailed development, partnering and/or commercialization strategies.

Generating predictions for success

As the disease landscape grows in complexity, early identification of targets that will be most successful becomes even more important. Combining broad, robust sources of evidence with advanced analytics and expertise will help to generate predictions and systematically prioritize indications across your research portfolio, ultimately setting up your drug development program for success.

Confidently prioritize indications and move into new markets. **Contact our bioinformatics team to learn more.**

References

1. National Cancer Institute Surveillance, Epidemiology, and End Results Program. NIH, [online], Available at: **https://seer.cancer.gov/**. (accessed: May 9, 2021).
2. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2): 273–286. doi: 10.1093/biostatistics/kxx069
3. 2020 CMR Pharmaceutical R&D Factbook (2021). Clarivate, [online], Available at: **https://discover.clarivate.com/2020RDFactbook**. (accessed: June 14, 2021)
4. Deloitte Centre for Health Solutions. (May 2021). Deloitte, [online], Available at: **https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-measuring-the-return-from-pharmaceutical-innovation-2021.pdf**. (accessed June 15, 2021).

About Clarivate

Clarivate™ is a global leader in providing solutions to accelerate the lifecycle of innovation. Our bold mission is to help customers solve some of the world's most complex problems by providing actionable information and insights that reduce the time from new ideas to life-changing inventions in the areas of science and intellectual property. We help customers discover, protect and commercialize their inventions using our trusted subscription and technology-based solutions coupled with deep domain expertise. For more information, please visit **https://clarivate.com/**.