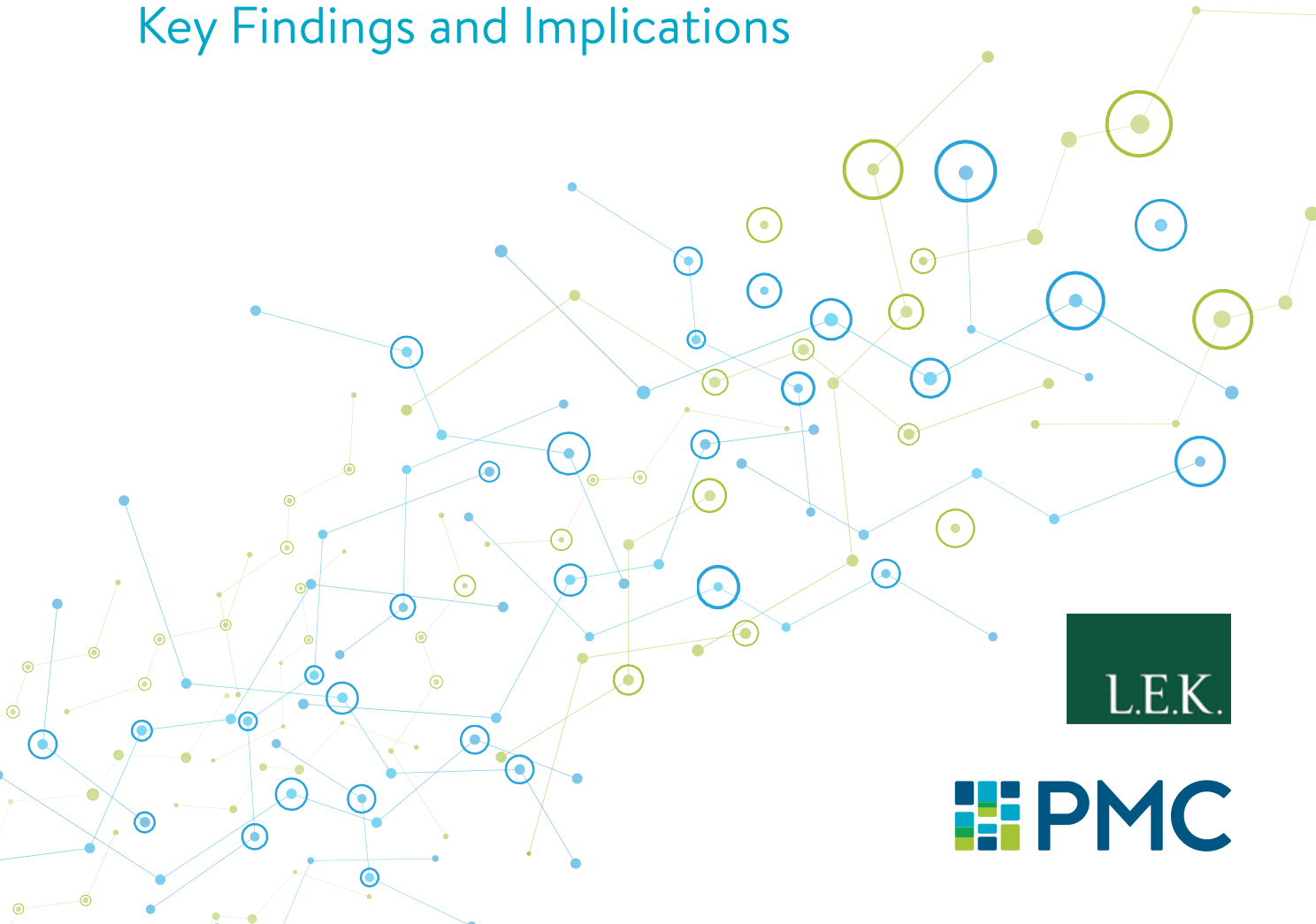
THE EVOLUTION OF BIOMARKER USE IN CLINICAL TRIALS FOR CANCER TREATMENTS

Key Findings and Implications



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PMC

Understanding the biomarker landscape, including clinical research activity, is critical as multiple stakeholders align themselves with the latest science.

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FOREWORD

When the Personalized Medicine Coalition (PMC) first published *The Case for Personalized Medicine* in 2006, the pharmaceutical industry was skeptical that it could or should develop drugs for subpopulations based on identifiable biomarkers. Outside of a small community of molecular biologists steeped in the knowledge of pharmacogenomics, a field that suggested that scientists could identify which patients a drug would work for, personalized medicine was a daunting concept, especially to those in the industry with a more commercial focus. When PMC gave its first award for leadership in personalized medicine to Janet Woodcock, Director of the Center for Drug Evaluation and Research at the U.S. Food and Drug Administration in 2005, she told us that she was "much more radical" than industry executives in understanding the implications of the new biomedical discoveries and new technologies that were then coming at a very rapid pace.

She was not wrong.

The industry's skepticism in 2005 derived both from a then limited appreciation of human heterogeneity at the molecular level as well as a business model that assumed that it should only develop drugs for "all comers," even if they only worked for subsets of the public — and that it could sell them for relatively low prices.

That challenge was compounded by an unclear regulatory system that inhibited integrating diagnostics into health care; by an overtaxed reimbursement system that was slow to comprehend the value of diagnostics, not to mention the necessarily higher prices for targeted drugs for smaller populations; and by the fact that most health care providers were trained before the human genome was mapped, which limited their appreciation of the new science and technologies that underpinned personalized medicine and, in turn, their willingness to make the necessary changes to integrate it into health care.

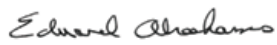
Suffice it to say that the business, policy, and educational challenges have not disappeared and will get worse if price controls based on population averages are put in place, though the industry's skepticism has, especially in oncology, all but

been eradicated as it has embraced the principles of personalized medicine. In 2005, personalized medicines, that is drugs that include biomarker strategies in their respective labels, represented only five percent of the new molecular entities approved by the U.S. Food and Drug Administration.

Last year, the figure was 42 percent, with most of the new approvals coming in oncology with enormous significance for the future of cancer care.

The Evolution of Biomarker Use in Clinical Trials for Cancer Treatments: Key Findings and Implications documents the industry's increasing commitment to developing personalized medicines in oncology. Written by Alex Vadas, T.J. Bilodeau, and Chintan Oza in L.E.K. Consulting's Life Sciences & Pharma practice, the study is the first comprehensive quantitative examination of a cancer biomarker database. Whereas previous analyses of the pharmaceutical pipeline, including the one PMC commissioned five years ago, relied on impressionistic survey data, this more definitive study analyzes the Aggregate Analysis of Clinical Trials, a cloud-based platform on which all clinical trials are registered.

Among the most significant findings are that 55 percent of all oncology trials in 2018 involved the use of biomarkers, as compared with 15 percent in 2000; that breast, lung, leukemia, lymphoma, melanoma, and prostate cancer trials are the most likely candidates to include biomarker strategies; that there is a new focus on pan-tumor biomarkers; and that, most significantly, the accelerating shift in drug development documented in the study has profound implications for key stakeholders across the health care spectrum, including the pharmaceutical and diagnostic industries, providers, payers, and, most importantly, patients, who, in the future, will benefit from earlier detection and more effective treatments because responders and non-responders can be identified, making drugs safer, more effective, and, over time, potentially less expensive for systems that incorporate personalized medicine.



President
Personalized Medicine Coalition

The increase in the percentage of oncology clinical trials with biomarkers has implications for every stakeholder within the health care system.

THE EVOLUTION OF BIOMARKER USE IN CLINICAL TRIALS FOR CANCER TREATMENTS

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BACKGROUND

Biomarkers have played an increasingly prominent role in drug development and the broader cancer patient journey over the past 15–20 years. Biomarkers are used across all stages of drug development, ranging from enrichment, stratification, and patient selection to safety, efficacy, and performance assessment. While some clinical trials recruit patients based on specific biomarker presence ("enrichment") and file for a companion diagnostics label, other trials examine specific biomarkers for research use to enable internal decision-making and to build clinico-genomic datasets. Oncology drug approvals are on the rise, representing 16 out of 59 of the U.S. Food and Drug Administration's new molecular entity (NME) approvals (~27 percent) in 2018 compared with nine out of 41 (~22 percent) in 2014. Furthermore, the percentage of personalized medicines gaining FDA approval has been growing over the past five years, from ~21 percent of all NME approvals in 2014 to ~42 percent in 2018.[1] Biomarkers are critical in the development of personalized medicines and have added more complexity to clinical trial design, execution, and data analysis.

Understanding the biomarker landscape, including clinical research activity, is critical as health systems and pharmaceutical R & D departments align themselves with the latest science. However, understanding biomarker strategies in the clinical pipeline requires tedious manual review of trial protocols. Biomarker data are not reported in a consistent manner across clinical trials (e.g., varying biomarker names; failure to report specific biomarkers being assessed, especially for early-stage trials). To facilitate the analysis of biomarker trial data, we have created a comprehensive cancer biomarker database leveraging the Aggregate Analysis of ClinicalTrials.gov (AACT) database that enables both macro and deep-dive analyses for trends in biomarker use over time. The increase in the percentage of oncology clinical trials with biomarkers has implications for every stakeholder within the health care system; therefore, it is critical for each stakeholder to align itself with the evolving paradigm of biomarker-driven personalized medicine.

1 Pritchard, D., Wells, C. "Raising the Bar: FDA Accelerates the Push Toward Personalized Medicine. *J. Precision Medicine*, 5;2, pp. 36–39.

METHODS

To generate these critical insights on macro biomarker trends, we explored the entirety of oncology clinical trials registered on ClinicalTrials.gov using a combination of automated analytical techniques and manual curation. First, we focused on searching the AACT database (~281,500 clinical trials) for ~2,500 oncology drugs from 2000 to 2018 for the inclusion of biomarkers. A defined list of biomarkers (including various synonyms) was created based on a variety of input sources to query the trials.[2] This yielded ~11,000 oncology clinical trials using biomarkers for any purpose. These ~11,000 clinical trials were analyzed to gain useful insights, including macro trends in biomarker use over time; biomarker use by tumor type; utilization trends for specific biomarkers; number of biomarkers used per trial; trial sponsor; and several other findings, many of which are discussed in this report.

2 We needed to query for the same biomarker using a range of synonyms (e.g., HER2, HER-2/neu, and ERBB2).

SUMMARY OF FINDINGS

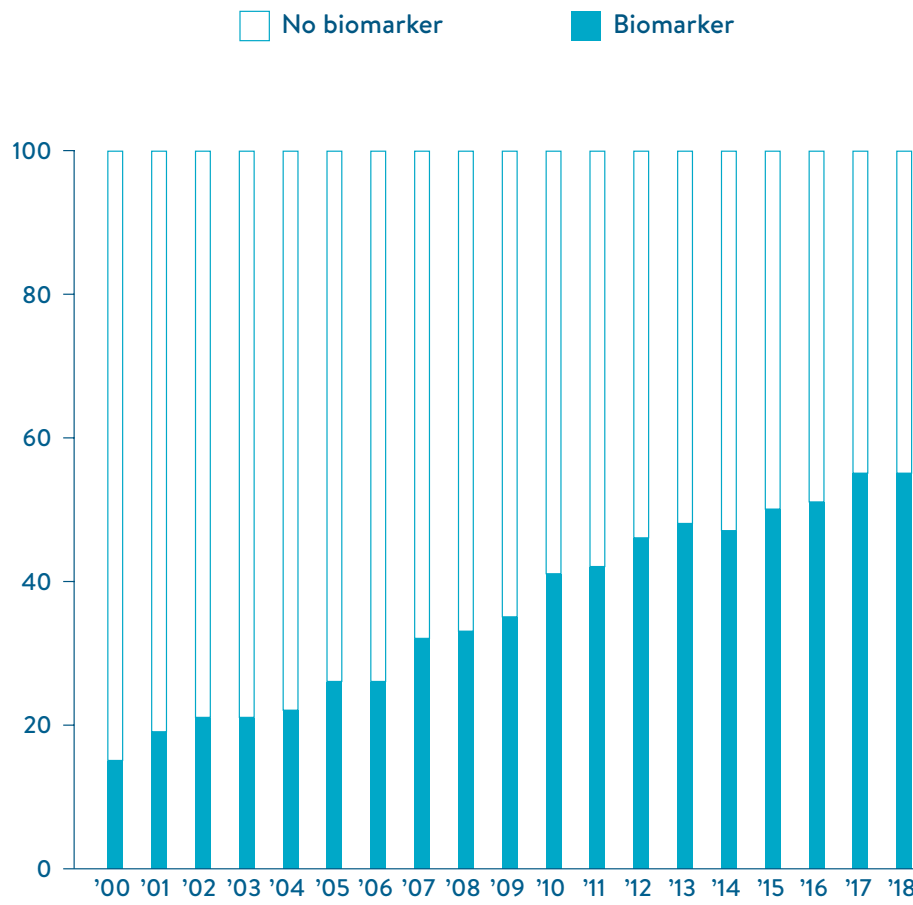
- The number and percentage of oncology clinical trials that include biomarkers have grown substantially: 55 percent of all oncology trials in 2018 involved the use of biomarkers, as compared with 15 percent in 2000 (a 17 percent compound annual growth rate).
- Breast (69 percent), lung (66 percent), leukemia (64 percent), lymphoma (57 percent), melanoma (74 percent), and prostate (86 percent)[3] are the most common tumors exploring biomarkers.
- Biomarker trial strategy has become more complex over time, and more than 50 percent of biomarker trials now examine two or more biomarkers per trial; many trials without a biomarker are for exploring a variety of chemotherapy regimens.
- Biomarkers such as PD-1/PD-L1/2, ALK, TIL, CD4, MRD, and BRAF have shown the fastest growth in the past four years.
- There is an emergence of trials around pan-tumor biomarkers (e.g., MSI and NTRK), reflecting the interest in biomarker-defined cancer indications.
- Roche/Genentech, Novartis, AstraZeneca/MedImmune, and Bristol-Myers Squibb/Celgene, along with the National Cancer Institute and MD Anderson Cancer Center, sponsored or collaborated on the largest number of biomarker-based clinical trials between 2000–2018.
- Growth in the importance of biomarkers will have a major impact on almost all key stakeholders across the health care continuum, including the biopharmaceutical industry (e.g., research and commercial decision-making); providers (e.g., building precision medicine capabilities); payers (e.g., enabling broad coverage for biomarker profiling); diagnostic laboratories and test developers (e.g., scaling, interpreting for clinical decision support, enhancing efficiencies through techniques such as sample-sparing and multi-plexing); and, most important, patients, who will get more effective treatments personalized to their unique medical needs.

3 Percentage of 2018 clinical trials with biomarkers.

RESULTS IN DEPTH

There has been a growing use of biomarkers in clinical trials, and ~55 percent of all oncology clinical trials in 2018 involved the use of biomarkers, as compared with ~15 percent in 2000 (Figure 1A). Our study included all oncology therapy trials using chemotherapies and non-targeted therapies, which are less likely to use biomarker-focused approaches. While there has been a ~9 percent compound annual growth rate (CAGR) for total oncology clinical trials since 2000, trials involving biomarkers grew at nearly twice this rate, at ~17 percent CAGR, during the same period (Figure 1B). This study focused exclusively on oncology clinical trials; however, a similar trend toward increased use of biomarkers has been observed across other therapeutic areas. Recent advancements in tumor biology, assay techniques, and tumor profiling solutions have influenced clinical trial design, especially in terms of the number of biomarkers tested in a trial. Almost half of the total trials with biomarkers specifically highlighted interrogation of two or more biomarkers in 2018, compared with just ~14 percent in 2000 (Figure 1B).

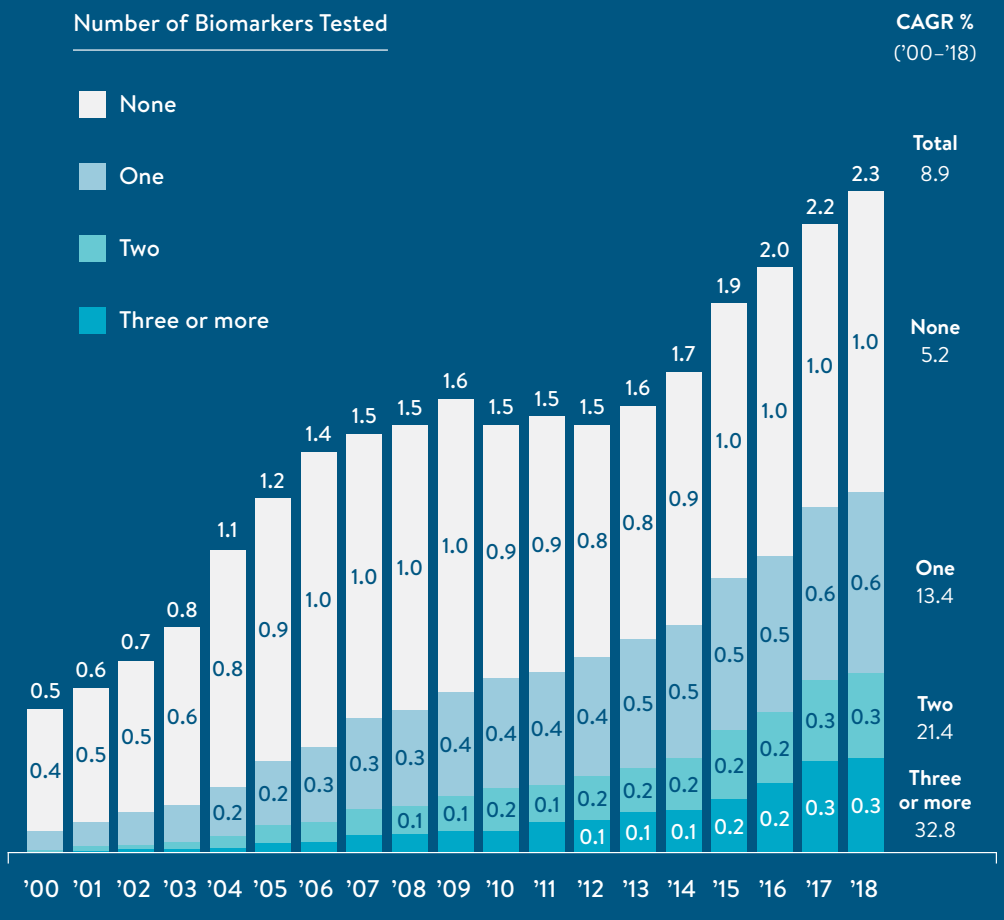
FIGURE 1A: Percentage of oncology trials, by use of biomarkers (2000–2018)



Sources: AACT; L.E.K. biomarker database

FIGURE 1B: Oncology clinical trials, by use of biomarkers (2000–2018)

Thousands of clinical trial starts by start year*



Note: *Number of biomarkers for trials that include both unspecified and specified biomarkers are counted as per the number of specified biomarkers; trials with only unspecified biomarkers are counted under one biomarker.

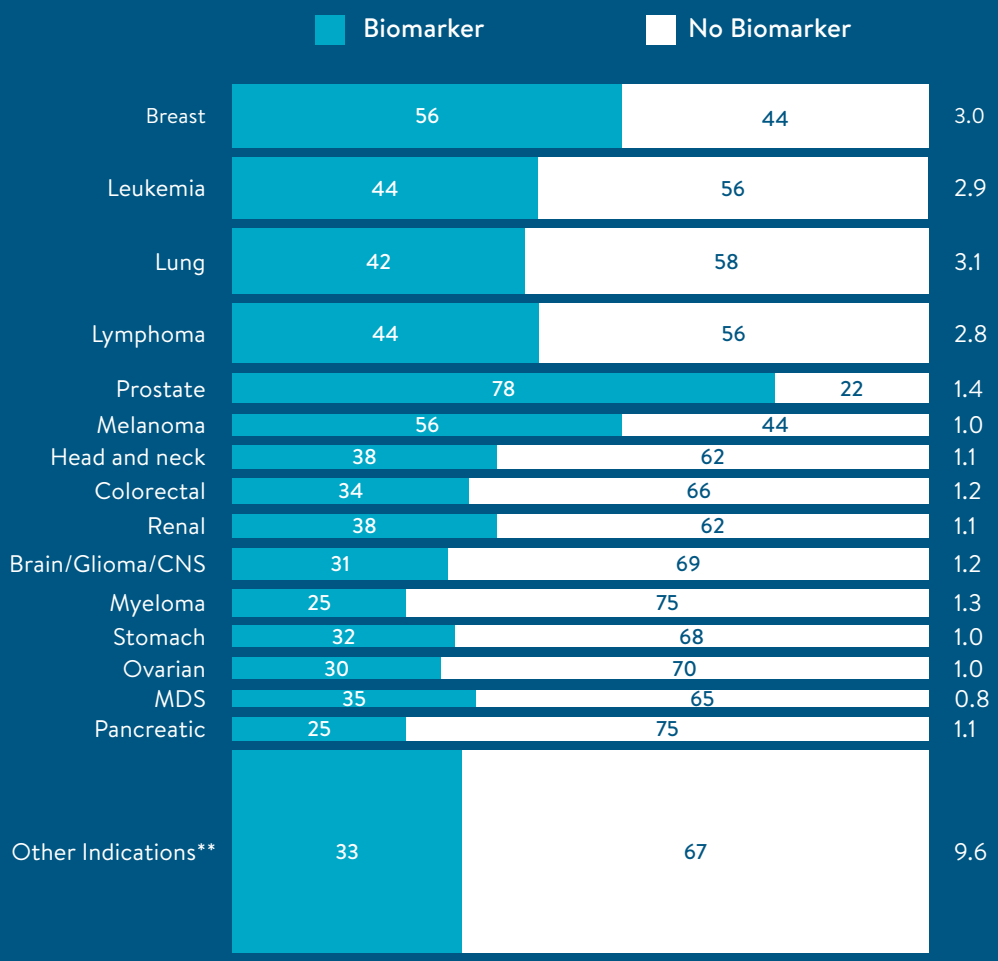
Sources: AACT; L.E.K. biomarker database

The future of cancer care is expected to be profoundly influenced by the use of biomarkers that will guide researchers and physicians at every stage from drug development to disease management.

Overall, biomarkers are being explored across all cancers, ranging from 25 percent to 60 percent of trials from 2000 to 2018, although use is highest in breast, leukemia, lung, lymphoma, prostate, melanoma, and head and neck cancers (Figure 2). Growth in biomarker trials since 2000 has been significant across most cancers, with lung notably outpacing others, where it has doubled biomarker trial count in the past five years alone (Figure 3).

FIGURE 2: Oncology clinical trials, by indication and biomarker use (2000–2018)

Percentage of cumulative trials started between 2000 and 2018*



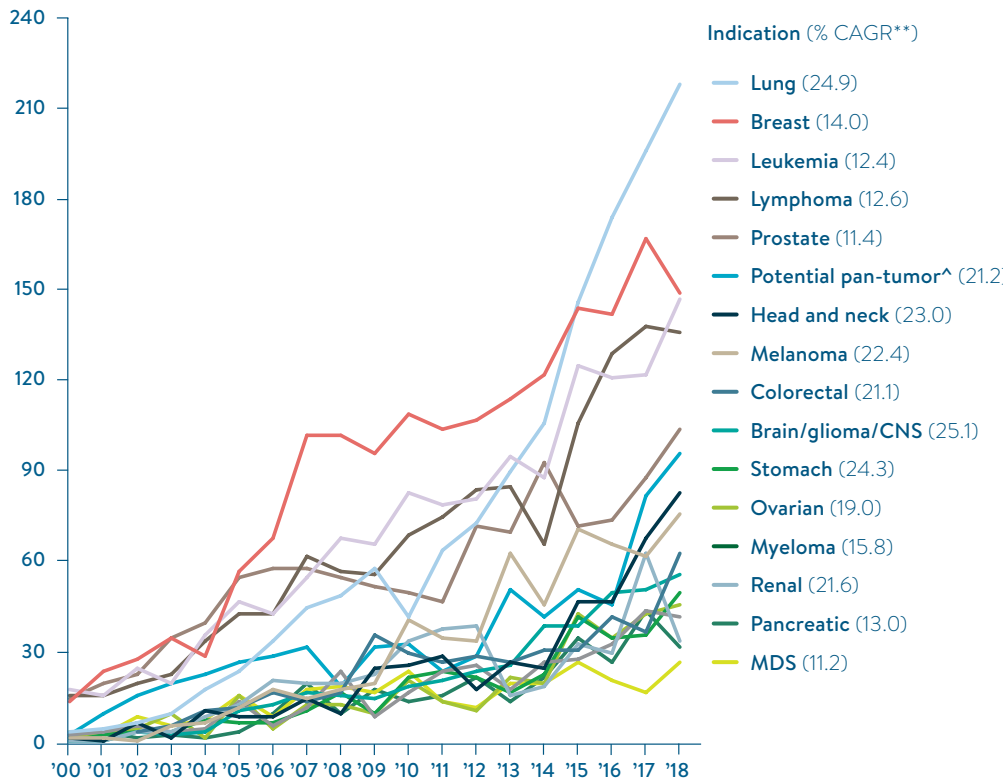
Note: *Trials looking at two or more indications are repeat counted for each indication.

**"Other indications" includes those indications not shown on the bar graph as well as tumor-agnostic trials that do not specify any tumor type; if a trial lists both specified and unspecified tumor types, then it would be counted under each of the specified tumor types.

Sources: AACT; L.E.K. biomarker database

FIGURE 3: Oncology biomarker clinical trials, by indication (2000–2018)

Number of clinical trial starts by start year*



Note: *Trials looking at two or more indications are repeat counted for each indication.
**% Indicates CAGR 2000–2018.
^ Potential pan-tumor biomarker trials were determined based on a proxy of trial activity that could potentially lead to a pan-tumor label and included oncology biomarker clinical trials in Phase 2,3 or 4 with >five specified tumors per trial or <five tumors per trial but including a general indication term (e.g., cancer, malignancies, metastasis/metastases, oncology, neoplasm, tumour/tumor).

Sources: AACT; L.E.K. biomarker database

Biomarkers tested in clinical trials are driven by the mechanisms targeted by precision therapies and immunotherapies, and also include prognostic and monitoring biomarkers. For example, HER2, EGFR, KRAS, BRCA1/2, and PD1/PD-L1 are biomarkers closely linked to therapeutic mechanisms in cancers such as breast cancer, non-small cell lung cancer, and ovarian cancer. MRD and PSA are key biomarkers for monitoring in heme and prostate cancers, respectively (Figures 4, 5). The biopharmaceutical industry has also increased its consideration of less common biomarkers, which are classified as "Other" in Figure 5.

There has also been significant growth in trials exploring pan-tumor biomarkers including MSI and NTRK, both of which are associated with pan-tumor indication approvals; for pembrolizumab (MSI) and larotrectinib and entrectinib (NTRK). For example, in the past five years, there were 31 trials conducted for the NTRK gene fusion biomarker and 63 trials for MSI. Other potential pan-tumor biomarkers, including TMB and FGFR, are in trials that could result in future pan-tumor indications (Figure 4). These trends clearly reflect advances in the use of biomarkers to guide personalized drug development independent of the more traditional organ-specific clinical trial approaches.

FIGURE 4: Top biomarkers used, by indication and years

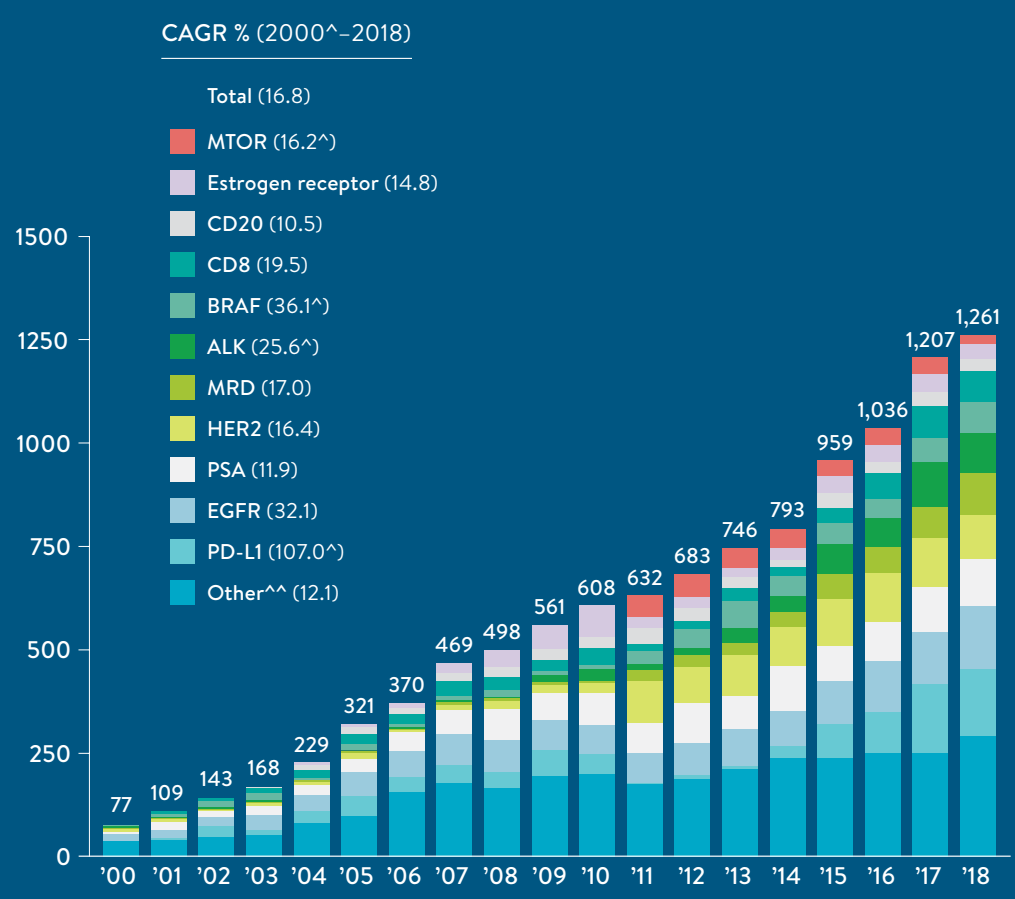
	2000–2018			2016–2018**		
Breast	HER2	ER*	PR*	Ki67	PD-L1	TILs
Leukemia	MRD	BCR-ABL1	FLT3	CD19	BTK	TP53
Lung	EGFR	ALK	PD-L1	ROS1	KRAS	PD1
Lymphoma	CD20	CD4	MRD	CD19	MYC	CD30
Prostate	PSA	AR	CTC	ATM	BRCA2	BRCA1
Melanoma	BRAF	CD8	TIL	PD-L1	PD1	CD4
Head & neck	HPV	EGFR	p16	PD-L1	CD8	TILs
Colorectal	KRAS	EGFR	BRAF	MSI	NRAS	CD8
Renal	MTOR	VEGF	EGFR	PD-L1	CD8	PD1
Brain/glioma/CNS	EGFR	MTOR	IDH1/2	CD4	BRAF	CD8
Myeloma	MRD	HLA-A	PSA	LDH	IL-6	EGFR
Stomach	HER2	KIT	EGFR	PD-L1	TILs	PD1
Ovarian	BRCA1	BRCA2	CD8	PD-L1	TILs	CD8
MDS*	HLA-A	MRD	FLT3	CD4	CD8	CD3
Pancreatic	EGFR	KRAS	PSA	CD8	PD-L1	IFN
Pan-tumor	MSI^	NTRK^	TMB	FGFR		

Note: *ER = Estrogen receptor; PR = progesterone receptor; MDS = myelodysplastic syndromes.
**Includes biomarkers not already included in top 3 from 2000–2018.
^Biomarkers with therapies approved for pan-tumor use.

Sources: AACT; L.E.K. biomarker database

FIGURE 5: Biomarkers examined in all clinical trials with top 11 featured,* by year (2000–2018)

Number of clinical trial starts by start year**



Note: *Top 11 are biomarkers used in >400 trials during 2000–2018.
**Trials examining two or more biomarkers are repeat counted for each biomarker.
^CAGR adjusted based on first available year of biomarker trial (MTOR from 2002–2018, BRAF from 2004–2018, ALK from 2001–2018, PD-L1 from 2011–18; all others from 2000–2018).
^^"Other" includes all other biomarkers (including ones examined in <400 trials and unspecified) during 2000–2018.

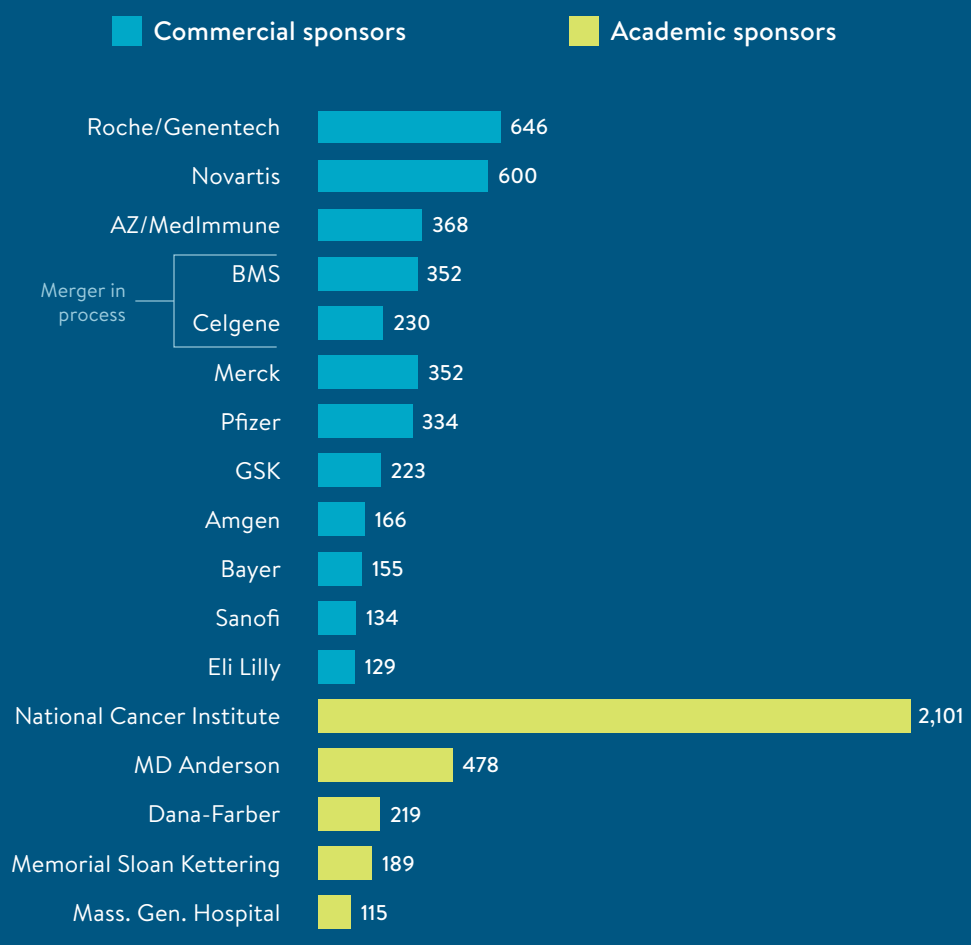
Sources: AACT; L.E.K. biomarker database

Ultimately, irrespective of the rationale, biomarker testing signifies a critical component in cancer research, clinical development, and treatment management.

Seventeen organizations, including five academic centers, have sponsored or co-sponsored 100-plus oncology trials involving biomarkers. Unsurprisingly, the National Cancer Institute, with dedicated research support to investigate biomarkers for targeted therapies along with a wide network of research laboratories and data centers, is leading the way in collaborating on or sponsoring oncology biomarker trials throughout the nation. The biopharmaceutical companies that pursued the most biomarker trials between 2000–2018 are Roche/Genentech, Novartis, AstraZeneca/MedImmune, Bristol-Myers Squibb/Celgene, Merck, and Pfizer. Their focus on biomarkers during this time period was likely driven by their targeted therapy and immunotherapy portfolios and disease area focus (Figure 6).

FIGURE 6: Organizations involved in 100+ oncology biomarker trials, by type (2000–2018)

Number of clinical trial starts*



Note: *Trials that are sponsored by more than one organization are repeat counted.

Sources: AACT; L.E.K. biomarker database

CONCLUSION

Biomarkers have become highly valuable in driving oncology research and development and the commercialization of targeted therapies, and will continue to have significant implications for all stakeholders across the health care continuum. In oncology specifically, the posture toward biomarker development for innovative oncology therapies is becoming the norm versus the exception, and the industry will need to adapt to this evolving paradigm of personalized medicine.

Biopharmaceutical companies have incorporated biomarker strategies to drive their research and commercial operations. Biomarkers are used to optimize their targeted therapy portfolios, make clinical development decisions, access and preserve bio-specimens, build and mine scaled clinico-genomic datasets, segment commercial markets, develop market access and pricing strategies for biomarker-driven targeted therapies, and pursue broader collaborations with academic and diagnostic partners.

It will be critical for health care providers to prioritize enhancing precision medicine capabilities, including biomarker profiling as well as data management and interpretation infrastructure to enable precision medicine care delivery.

Diagnostic companies will play a major role in actively collaborating with biopharmaceutical companies and providers. Multi-plexing, sample-sparing, and liquid biopsy techniques that enable broader testing from smaller amounts of tissue or plasma samples may play a prominent role.

Payers will need to enable reimbursement that includes broader coverage of biomarker testing.

Ultimately, biomarker-driven personalized medicine approaches will lead to better patient outcomes by enabling early detection; identifying treatment responders; and monitoring treatment, response, and targeted therapeutic effect.

Regulators will need to provide comprehensive guidance on sample quality and testing, further simplify the approval process for companion diagnostics, and standardize guidance around the use of personal data for research purposes.

Patients may request advanced testing and ask their providers to use sample-sparing approaches where possible, and may contribute their de-identified data for clinical research.

Ultimately, biomarker-driven personalized medicine approaches will lead to better patient outcomes by enabling early detection; identifying treatment responders; and monitoring treatment, response, and targeted therapeutic effect. The future of cancer care is expected to be profoundly influenced by the use of biomarkers that will guide researchers and physicians at every stage from drug development to disease management.

METHODOLOGICAL NOTES

Biomarker clinical trial data are unstructured and lack standardization for biomarker description and use. Trial sponsors may mention the use of biomarkers in general trial descriptions, inclusion/exclusion criteria, outcome measures, or other locations, and may use different names or acronyms to describe the same biomarkers, making it difficult to search and analyze publicly available datasets like the AACT. The AACT, developed by the Clinical Trials Transformation Initiative, contains information about every clinical study registered at ClinicalTrials.gov, including more than 260,000 trials since 2000. To study the use of biomarkers in oncology clinical trials over time (2000–2018), a list of ~2,500 oncology drugs was created by conducting a specific search for drug disease group ("anti-cancer products") and drug disease status ("Phase 1" through "Launched," including "Not Applicable") using the PharmaProjects database.

Next, a comprehensive list of ~300 biomarkers was created by leveraging multiple sources, including (a) biomarkers examined in diagnostic tests per different oncology guidelines across different tumors; (b) scientific and clinical literature describing biomarker use across different tumors; and (c) prior L.E.K. Consulting work in oncology and biomarkers. All known variations of names for drugs and biomarkers were included in the analysis.

Then, the AACT database was linked to an analytical workflow in Alteryx to perform text-based analysis in the clinical trial fields, such as eligibility criteria, outcome classifications, trial descriptions, and design outcome measures. The database was first analyzed for clinical trials using a text search for the ~2,500 oncology drugs (it identified ~35,000 out of more than 260,000 trials).

Subsequently, trials involving biomarkers were identified by performing a text search across all the database fields (e.g., biomarkers looked at as eligibility criteria or as outcome measures or trials stating biomarker analysis will be undertaken without listing any specific biomarker), resulting in ~11,000 trials (out of ~35,000).

Trials were grouped by tumor type, which was determined by conducting keyword searches within indication fields of each trial protocol. This led to trials being grouped into 36 different tumor types (or "other") to allow analysis of the database at an indication level.

Given the large size of the resulting dataset, Tableau was used to visualize the data and calculate cross tabulations. Any duplicate trial listings or biomarker matches were further removed when looking at the data in Tableau. Phase 2/3 trials were grouped as Phase 2, and Phase 1/2 trials were grouped as Phase 1. Trials looking at multiple indications were repeat counted for each indication, where applicable. The resulting database contained the following clinical trial information: number of trials with biomarkers; number of biomarkers per trial; biomarker names by trial; biomarker use by tumor type; therapy/intervention; trial sponsor; trial start and completion dates; trial location; trial phase; trial enrollment size; and outcome measures. Therefore, this comprehensive biomarker database can be used to conduct several data analyses to assess key macro trends as well as specific deep-dive analyses across multiple dimensions over time.

ABOUT US

The Personalized Medicine Coalition, representing innovators, scientists, patients, providers, and payers, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.

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