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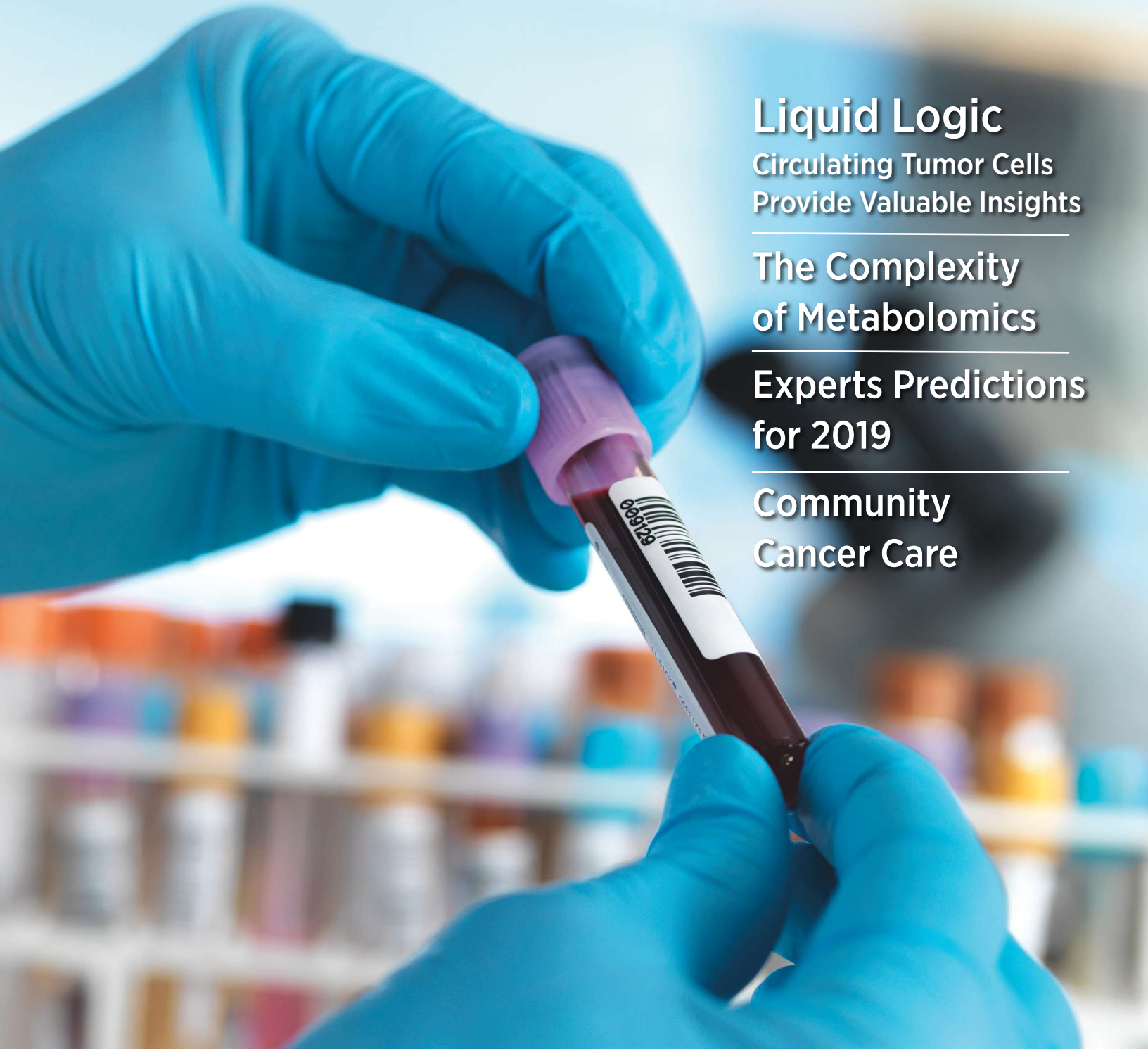
Clinical OMICs

Molecular Diagnostics in Personalized Medicine



Liquid Logic

Circulating Tumor Cells Provide Valuable Insights

The Complexity of Metabolomics

Experts Predictions for 2019

Community Cancer Care

Unlocking the Value of Complex Biomarker Data

By Scott Marshall, Ph.D., Managing Director, Translational Informatics and Diagnostic Sciences; Tobias Guennel, Ph.D., Senior Director, Translational Informatics and Biometrics; and Cliff Culver, SVP, Precision for Medicine

Introduction

Modern biomarker-guided drug development has been driven, in part, by the need to target specific patient populations and create efficient, cost-effective methods for developing transformative therapeutics. A key component of the discovery process involves characterizing the cascade of biological pathways and processes that ultimately drive response and potentially define patient populations.

Sponsors frequently invest substantial time and capital into advancing novel technologies and approaches in this realm, particularly as the cost of using complex assays to interrogate biological pathways decreases. And yet, we have only uncovered the tip of the iceberg when it comes to utilizing the massive volumes of data these new technologies create. In particular, we are in the early stages of effectively aggregating and harmonizing this data to make it actionable. Additionally, the rise of platform licensing and partnership structures has led to the prioritization of enabling the efficient consumption of complex analytical results and establishing a foundation to foster collaborative analyses to fuel the drug development process.

In this article, we explore biomarker data trends and challenges, and share how drug developers, translational scientists, and clinical researchers evaluating biomarkers in early-phase studies can:

- Move beyond data overload and leverage cutting-edge technologies to seamlessly transform millions of data points into actionable insights
- Harness advanced informatics and visualization tools to harmonize disparate sources of biomarker data and warehouse them for effective on-study use (e.g., dose selection), as well as downstream use
- Build flexibility, efficiency, and compliance into the rapidly evolving biomarker-informed development process
- Accelerate go/no-go decision-making to reduce time and cost

Biomarkers in Clinical Trials

Since 2013, there has been a sharp increase in the number of clinical trials citing a biomarker-guided precision medicine design.[1] Evaluating biomarkers in clinical trials and integrating specialty lab data (e.g., flow cytometry, gene expression profiling, immunosequencing) with pharmacokinetics, safety lab, and clinical data can provide a more comprehensive picture for assessing the efficacy, pharmacodynamic effect, and safety of an investigative compound. A recent report revealed that drugs developed using a precision medicine design had a higher likelihood of launch across all therapeutic areas, with the most significant difference in oncology (*see Figure 1*).

The message: The impact of a precision medicine design may be even more powerful when biomarkers are used for patient selection. A study of clinical development success rates over the 10-year period from 2006 to 2015 demonstrated that the use of biomarkers for patient selection was associated with a three-fold increase in the likelihood of success from Phase 1 to approval.[2]

An ever-growing set of biomarker assays are available,

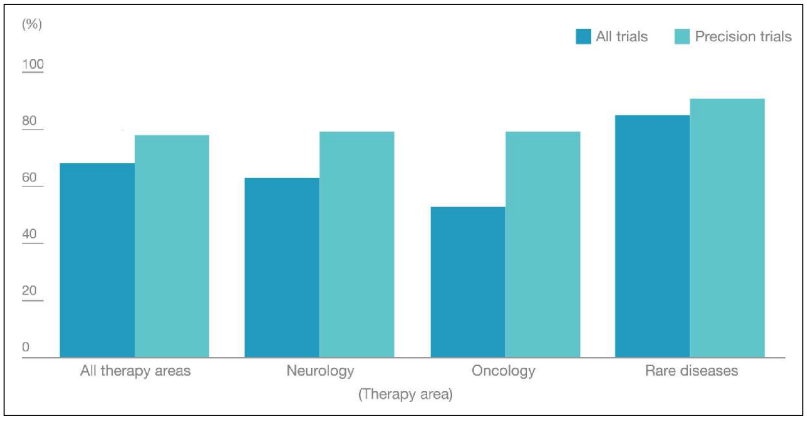


Figure 1. Average Gain for Precision Medicine Trials: 15 Percentage Points

Trialtrove | Pharmaintelligence, 2018. Data: 2012-2017. Adapted from The Economist Intelligence Group. The Innovation Imperative: The Future of Drug Development | Part I: Research Methods and Findings.

ranging from targeted genomic panels to high-content or high-throughput experiments. These assays have a broad range of applications—addressing patient selection, characterizing mechanism of action (MoA), guiding dosing, and optimizing study design. Technologies are evolving as well, and data are now being generated at unprecedented rates from flow cytometry, next-generation sequencing, immunophenotyping, mutational analysis, gene or protein expression, multiplexed immunohistochemistry, circulating tumor cells, and more. Specialized labs and associated technologies have emerged to deliver on these assays and many have had to develop proprietary technology, methods, or panels. The diversity and complexity of biomarker assays is further complicated by the fact that the resulting data are generated in different formats and data structures, creating challenges around data harmonization, interpretation, and accessibility.

As in most industries today, the generation of significant volumes of data in biopharmaceuticals has become more cost-effective and more critical for driving decisions that impact the success of a drug development program. However, there has historically been no efficient way to leverage all of the data generated. Instead, data is generated, but not managed and analyzed efficiently due to the limitations of teams and the lack of appropriate technology. According to a survey by *Forbes*,[3] nearly 80% of scientist time is spent collecting, cleaning, and organizing datasets. With only a fraction of generated data being leveraged, there is a tremendous opportunity to create additional value and insights if these data can be made seamlessly accessible for visualization, large-scale analytics, and, ultimately, sharing.

From Biomarker Data to a Biomarker-Guided Drug Development Data Asset

In order to optimize value creation from generated data, drug developers and innovators need to be able to perform rapid data interrogation within and across platforms, trials, geographies, and even companies. Data interrogation capability, which can be either visual or analytic, facilitates hypothesis rule out, as well as generation of novel hypotheses to shape and guide a drug development program. Beyond data interrogation, the biomarker data management system must also be able to disseminate information seamlessly within and across organizations.

Of course, data interrogation and analysis first requires a harmonized data set that is quality controlled and correctly mapped together. This task becomes increasingly complex with each incremental assay, each additional lab, and each subsequent study. In fact, a typical Phase 1 immuno-oncology study with a standard assay package may generate >10 million data points. The level of effort required here would easily consume multiple advanced data scientists with backgrounds ranging from the computational to biological sciences. Automation is almost a requirement to do this effectively particularly given the near real-time turnaround needed to support on-study decisions.

In development programs where biomarkers are used to support go/no-go decisions between trial phases, the lack of tight integration between clinical operations and biomarker data can lead to longer timelines, increased costs and even delayed approvals. The right technology must also be able to organize these data effectively and efficiently as part of end-of-study activities and regulatory submissions.

With the recent explosion of partnerships and licensing deals and the emergence of novel combination therapies, the ability to share data within and across both platforms and organizations will be critical to realizing value. Organizations that are able to provide access to complex, organized data sets can help convey early signs of positive biological response in early-phase trials, which can further support increased partnership, licensing, and fundraising activities. Increasingly, early biomarker data is being used to inform the viability of novel therapeutics. Whether it enhances the profile, or simply acts as the canary in the coal mine, these insights are transforming how investments are contemplated.

Tobias Guennel, Ph.D

Technologies That Are Driving Value

Today, technology platforms that are linking seamlessly across other technologies, such as electronic data capture (EDC) or laboratory information management systems (LIMS), have the potential to address key value drivers. To handle the complexity and throughput of biomarker assays and make data available to inform decision-making, these technology platforms must provide:

- Automated pipelines for the ingestion of data from an unlimited number of labs for all types of biomarker assays

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seksan Mongkhonkhamsao / Getty Images

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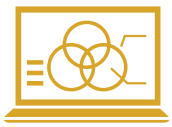
Cross-Study Profiling and Interrogation

- Enables rapid interrogation across multiple studies to assess certain biomarker-defined subpopulations
- Populations defined by decision rules on multiple biomarkers and even biomarker-derived signatures

Ability to link processed/quantified biomarker data to underlying raw biomarker data and clinical annotations from the EDC



Enables use of biomarker data in near real time to facilitate biomarker-guided decision-making

Rapid visual and analytical interrogation = interprelytics to rule out millions of hypotheses in seconds -> focus on the right hypotheses of interest

Features of an Ideal Biomarker Data Management Platform

- A centralized database for storage and access to all specialty lab data post-ingestion
- Data reconciliation capabilities to expedite historically time-consuming reconciliation activities between LIMS and EDC
- Assay-specific workflows and quality control parameters, as well as a capability to incorporate custom workflows
- Plug-in modules for translational research/biomarker data management
- Submission-ready datasets that comply with Clinical Data Interchange Standards Consortium (CDISC) standards and can be adapted to shifts in regulatory requirements
- Compatibility with other software tools (e.g., GraphPad Prism)

In addition, these technologies must have the capability to simultaneously integrate and deliver multiple workflows with dynamic reporting for real-time visual analytics, large-scale analytics and data sharing. This data integration capability supports key objectives, such as dose evaluation, multimarker biomarker signature development, biomarker-defined patient stratification, and real-time quality control analysis. It also provides valuable insight into pathways, networks, and compounds for drug positioning and future study design. The ability to visualize and analyze biomarker data through user-friendly, intuitive web-based tools enables sponsors, translational researchers, and clinical trial teams to harvest insights from all data sources to inform decision-making.

Conclusion

Delivering on the promise of precision medicine requires out-of-the-box thinking and informatics platforms designed to efficiently unlock the full potential of data collected. Just as EDC technology helped revolutionize clinical data management, technology-based solutions for biomarker data management will now become a requirement for modern clinical trial operations. However, technology alone is not enough.

Ultimately, success requires a cross-functional team, including data scientists, translational informaticians, biomarker data management programmers, data managers, and innovative data scientists, with the skill to design, validate, and operate technologies engineered specifically to address the challenges of biomarker data management in the new paradigm of biomarker-guided drug development. Combining cutting-edge technology with deep biomarker expertise facilitates flexibility, efficiency, and compliance, reducing cost and bridging the gap between translational researchers and clinical trial teams to optimize the development process.

The authors are part of a team at a biomarker research organization, Precision for Medicine, that developed a biomarker data management technology platform that ingests diverse data, harmonizes it and supports complex analysis in real time.

1 The Economist Intelligence Unit. The Innovation Imperative: The Future of Drug Development Part I: Research Methods and Findings.
2 David W Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay. Clinical Development Success Rates 2006-2015. (2016) A BIO Industry Analysis.
3 Press G. Cleaning Big Data: Most Time-Consuming, Least Enjoyable Data Science Task, Survey Says. March 23, 2016.