A convergence of biological data and computing power is yielding amazing technological progress in clinical research and development. Vast amounts of data, often from disparate sources, enable traditional treatment paradigms to transform into precision medicines that produce improved patient outcomes.

The field of oncology has been at the forefront of the precision medicine revolution, especially regarding the design and methodology of clinical trials (Blucher, 2017; Woodcock, 2017). This is largely because of the enhanced molecular characterization of tumors and more readily available high-throughput screening technologies that continue to propagate important developments in biomarker identification and validation. Precision oncology seeks to rationally select treatments for individual cancer patients based on their genetic information so as to provide the most accurate and effective treatment (Blucher, 2017; Shin, 2017). While the notion of precision oncology is not new (e.g., Gleevec [imatinib mesylate] for use in patients with BCR–ABL1-positive chronic myelogenous leukemia was approved by the FDA in 2001), constantly emerging biomarker data are enabling more precisely targeted therapeutics.

The rise of precision oncology has facilitated the approval of several new drugs. This includes the first ever approval of a drug (Keytruda [pembrolizumab]) to treat patients whose cancers have a specific genetic feature, rather than basing treatment on the location where the cancer originated (FDA, 2017). This approval represents a major shift in thinking by the FDA and set the precedent for drug developers pursuing this innovative pathway. Furthermore, as part of the FDA's Precision Medicine Initiative, the agency has issued two draft guidances and established the precisionFDA portal for oversight, analysis, and validation of approaches related to next-generation sequencing (NGS) tests that are used to distinguish genomic differences in individuals (FDA, 2016).

The cancer care landscape is quickly evolving to improve patient care. According to the American Society of Clinical Oncology’s (ASCO) State of Cancer Care in America: 2017 report, three important trends are driving this evolution (ASCO, 2017):
Precision medicine and immunotherapy have experienced massive research investments. This has propelled cancer care further in the direction of precision medicine, and there have been meaningful improvements in survival for patients with traditionally challenging diseases. For 2016, highlights included the FDA’s approval of the first NGS and liquid biopsy diagnostic tests as well as 16 new and expanded-use cancer therapies.

Real-world evidence and data sharing initiatives are more often being facilitated by various stakeholders. An important milestone was the passing of the 21st Century Cures Act, “which includes provisions to ensure that EHR [electronic health record] systems are interoperable and support the development of learning health care systems” (ASCO, 2017). Furthermore, major genomics projects are growing in number and scope. Major efforts include Genomics England’s 100,000 genomes project, the U.S. Department of Veterans Affairs Million Veteran Program, and AstraZeneca’s initiative to sequence 2 million genomes.

The completion of The Human Genome Project in 2003 provided scientists with the fundamental tool that has fueled the explosion of cancer biomarker discovery over the past 15 years. The Human Genome Project has combined with new technologies that allow biomarker identification to be conducted using high-throughput approaches (e.g., gene expression arrays and mass spectrometry) (Henry, 2012) to produce a flood of new biomarker data in the scientific literature. The success of precision oncology relies on the development of validated biomarkers that can be targeted with molecular therapies (Collins, 2015; Woodcock, 2017). Furthermore, increasing numbers of disparate data streams are generating large volumes of data that can inform precision oncology applications. A major challenge that drug developers face is how to seamlessly ingest, aggregate, integrate, and analyze these data sets in an easy-to-use workflow that can uncover meaningful relationships that will improve patient outcomes.

While new biomarker data has enabled an expanding number of precision oncology trials, sponsors are more frequently confronted with a new hurdle: an insufficient number of patients. Patient scarcity has become an issue because precision oncology trials are evaluating rare diseases with smaller subsets of patients (i.e., a smaller pool to begin with). In addition, there are record numbers of oncology clinical trials (often with the same target or pathway), meaning that sponsors are competing for patients from the same limited pool of potential recruits. For instance, in light of the recent successes with immunotherapies, there are an estimated 1,000+ immunotherapy clinical trials currently underway.

This dichotomy — abundance of disparate data versus patient scarcity — has generated a tension that can frustrate drug sponsors that are ready to test a new therapeutic but unable to recruit sufficient patients in a timely fashion.

Optimized clinical development technologies are key to supporting precision oncology trials. These technologies can harness a variety of disparate data sources at richer and greater volumes. They also aid in optimal site selection, patient recruitment, and innovative trial designs, such as those utilizing synthetic control arms (SCAs) which reuse subject level data from multiple historic clinical trials. The following sections of this paper discuss some of the hurdles and benefits associated with an abundance of disparate data and patient scarcity, followed by a short discussion of clinical development technologies in use to help sponsors overcome some of the current challenges in precision oncology.

**Scarcity of patients**

The increasingly targeted nature of precision drugs coupled with an escalating number of oncology clinical trials has created a patient
recruitment challenge, since the pool of eligible patients is much smaller than in trials for unselected patients (Kolata, 2017). This problem is exacerbated by more traditional barriers to patient recruitment, such as lack of encouragement or support from the physician, awareness of clinical trial design regarding placebo and standard-of-care treatment, and unrealistic inclusion/exclusion criteria (Stone, 2015). Overall, eligible patient pools that are more limited often mean that it will take sponsors longer to recruit an adequate number of patients and appropriately test their therapeutic through clinical development. Together, these factors increase the potential time to market and decrease the amount of time that a drug will have market exclusivity.

Recent developments in targeted drugs and immunotherapies have delivered significant benefit to cancer patients. However, these are two areas that exemplify the potential patient scarcity challenge. Below, we provide short discussions of targeted, immuno-oncology, and anti-metastatic therapies and how these areas are impacted by patient scarcity.

**Targeted Therapies**
Pathologic data have formed the backbone of cancer treatment decisions for decades. However, this paradigm has been evolving to include patient genetic and genomic information. This evolution has been a key development driving precision oncology, since many cancer mutations are extraordinarily rare and cannot be identified without appropriate genetic testing (Rehm, 2017; Peterson, 2017; Tuna, 2012). The identification of rare cancer mutations is challenging and requires the collection and analysis of genomic information from large patient populations. Armed with this information, drug sponsors can develop appropriate targeted cancer therapies that block the growth and spread of cancer by interfering with the specific molecular targets that are required for cancer cells to proliferate, thrive, and disseminate. Additionally, some cancers eventually develop resistance to targeted treatments and require combination therapies, further reducing the potential pool of relevant patients (NCI, 2017; Hanahan & Weinberg, 2011).

A study by Kavuri et al. (2015) highlights how rare cancer mutations can quickly erode a potential patient pool, and yet these limited patient populations may benefit even more from targeted therapies, since traditional treatment may not be effective in patients harboring certain rare mutations. In the study, the authors evaluated the impact of HER2 mutations in colorectal cancer (these mutations have been identified in only 7% of patients). Specifically, the investigators were interested in testing HER2-targeted therapy in samples that were resistant to cetuximab, since HER2 gene amplification is known to produce resistance to EGFR monoclonal antibodies (which cetuximab is). Of the 48 cetuximab-resistant colorectal samples tested, only four had HER2 mutations. The authors found that the samples with HER2 mutations required dual HER2 targeted therapy (with trastuzumab) plus an additional form of treatment (i.e., tyrosine kinase inhibitors) to produce tumor regression in a model of the disease (Kavuri, 2015).

Overall, it can be difficult to conduct standard clinical trials with rare cancers, but molecular profiling of cancers has offered a new avenue for developing precision oncology drugs. The implementation of new trial designs (basket trial and genetic marker designs) and the leveraging of clinical development technologies can more effectively facilitate identification and recruitment of the right patient population (Conley, 2016).

**Immu-no-oncology Therapies**
The basic premise underlying immuno-oncology therapies is that the immune system can destroy tumor cells if it can detect them. PD-L1 is a protein found in human cells that normally prevents the immune system from attacking other cells in the body. Tumor cells have cleverly adopted this protein as well, which allows them to evade detection by the immune system. Several FDA-approved drugs, (ipilimumab [Yervoy], pembrolizumab [Keytruda], and nivolumab [Opdivo]), commonly referred to as “checkpoint inhibitors,” unleash the patient’s own immune system to recognize and destroy tumor cells. These drugs have demonstrated phenomenal clinical activity across a variety of tumor types (Iwai, 2017; Hoos, 2016; Akbay, 2013).

However, the expression of checkpoint mediators and mutational load do not always correlate directly to efficacy (i.e., are not fully predictive), indicating that the complexity of the immune response is not fully understood. Overall, these novel therapies require an abundance of patient data, and identification of the subset of patients with the relevant biomarkers remains an immense challenge. Research is actively ongoing to enhance biomarker profiles that indicate a good match for specific therapeutic regimens (Gajewski, 2011; Rizvi, 2015; Mehnert, 2017). As the number of clinical trials in this area expands, and patients are increasingly segmented into specific groups, the patient pool available for clinical studies may continue to shrink.

**Anti-metastatic Therapies**
It has been recognized that for solid cancers, invasion and metastasis account for more than 90% of mortality (Sleeman, 2010). Traditionally, progression in solid cancer has been defined by tumor size and clinical endpoints linked to tumor shrinkage. However, these data are not always sufficient to infer whether there is significant clinical benefit, since these are only indirectly related to a cancer’s metastatic potential (Fernandes, 2015). A serious gap in the current anticancer armament is a category of anti-metastatic (or migrastatic) drugs (Gandalovičová, 2017; Fernandes, 2015). In addition to adjustments to the regulations governing approval of cancer therapies, development of anti-metastatic drugs will require massive amounts of data. A comprehensive understanding of the relevant signaling pathways, genomic stability, drug resistance, and tumor microenvironment for an individual patient will be required to
properly deliver the right therapy (Gandalovíčová, 2017; Sleeman, 2010; Steeg, 2016).

The abovementioned precision oncology approaches will continue to mature in the coming years and will undoubtedly transform cancer care. However, it is recognized that these approaches require ever more specific subsets of patients, and clinical successes will draw additional investment and clinical trials. These factors will likely contribute to perpetually shrinking patient pools that make it more difficult for sponsors to recruit sufficient patients in a timely manner.

**Clinical Technologies Address Patient Scarcity**

Medidata offers a number of solutions that help sponsors overcome the challenge of efficiently recruiting sufficient patients for their precision oncology trials. Operational Performance Analytics (OPAL) evaluates the clinical research study and site to analyze the root causes of subpar performance. Users can learn from prior successes and failures of research studies to understand where to improve (e.g., slow recruitment, poor data quality, long cycle times).

The use of Medidata Synthetic Control Arm enables better estimation of treatment effects from a single-arm trial and reduces the number of patients in control arms. In a recent study, the Medidata trial archive was used to develop a synthetic control arm for a Phase I/II single-arm trial in acute myeloid leukemia. The results demonstrate the successful utility of this approach by establishing early endpoints as predictors of long-term clinical outcomes (Berry, 2017).

**Abundance of disparate data**

Despite the enormous volumes of data that have arisen from basic and clinical research, relatively poor predictive ability remains when it comes to the correlation between biomarker status and relevant clinical response rate (Antolin, 2016; Anighoro, 2014). However, a wide array of disparate data are increasingly available, including traditional laboratory and physiological data, genomics, imaging data, and sensor data. Important insights can be gained from the integration of these data, potentially leading to a larger number of predictive biomarkers and with better predictive capacity.

Biomarkers remain the foundation of precision oncology drug development (Woodcock, 2017). The use of biomarkers can narrow a patient population to subsets that are most likely to experience clinical benefit from a treatment and facilitate patient recruitment. A recent study undertaken by biotech’s largest trade organization, the Biotechnology Innovation Organization (BIO), found that oncology drugs have the lowest likelihood of approval (LOA) from Phase I, at 5.1% compared to 11.9% for all indications outside of oncology and 26.1% for hematology. However, the advantage of using selection biomarkers was clearly demonstrated by raising the Phase I LOA to 25% (from 9.6%), and compared to other therapeutic areas, oncology had the highest first-cycle approval chance, at 79% (Thomas, 2016).

Biomarkers may also identify positive treatment effects without relying on traditional clinical endpoints used in standard-of-care practice. Thus, to maximize the potential success of a precision oncology application, it is necessary to develop a fundamental understanding from well-supported evidence.
information and validate biomarkers that will ideally provide high predictive capacity. However, the latter is not always a straightforward evaluation, since it can be difficult to obtain consistent and reliable information on potentially relevant biomarkers. New developments, such as the concept of a unified Cancer Targetome to aggregate drug-target interaction resources (Corsello, 2017), will increasingly facilitate precision oncology.

The integration of more reliable biomarker data with other data streams may prove to be an invaluable approach for developing novel therapies. Below, we discuss three areas that may benefit from the use of disparate data: drug repurposing, combination therapies, and real-world evidence.

**Drug Repurposing**

Bringing a new drug to market remains a risky and costly endeavor. The probability of progressing from Phase I to FDA approval has been estimated to be approximately 10% (Thomas, 2016), and the average cost is $2 billion to $3 billion (Nosengo, 2016). Furthermore, many potential drugs never reach the clinical testing stage (Corsello, 2017). Thus, the repurposing of existing drugs for new indications is a growing area of interest in the development of anticancer therapies, and it is a recognized strategy that has some successes (Bayat Mokhtari, 2017; Oprea, 2012; Azvolinsky, 2017; Coyle, 2016; Sun, 2016). Approximately 30 articles on cases of drug repurposing are published per month (a six-fold increase since 2011) (Nosengo, 2016). Overall, this approach can potentially shorten the time to market and lower the overall cost of drug development. Many of these agents have already been clinically tested, so information is available on their pharmacology, potential side effects, and formulation.

A common starting approach to drug repurposing is to identify FDA-approved drugs or drugs that failed and were abandoned in clinical development and screen them for activity against cancer cells. This can be achieved using low- and high-throughput screens, computational approaches, and even newer innovative methods, such as EHRs (Ketola, 2016; Zerbini, 2014; Hart, 2016; Xu, 2015). Extensive data analysis is required to maximize the success of a drug repurposing program, including an understanding of drug efficacy, patient responses, and potential toxicities. Applying advanced analytics to large volumes of disparate data helps identify novel possible uses for old or failed drugs (Chen, 2016). A potential computational approach is provided in the following figure. Overall, there is a multiplicity of opportunities for precision oncology to leverage existing drug data.

“With the expanding volume of available data and novel approaches to synthesize these data, new hypotheses can be generated and tested in a time- and cost-efficient manner.” – David Lee, chief data officer at Medidata.

**Combination Therapies**

Combination drug treatment is an important paradigm in cancer therapy. Using multiple therapies that additively or synergistically target key pathways can reduce the likelihood of drug resistance. It can also produce anticancer benefits, such as inhibiting tumor growth, arresting actively proliferating cells, and inducing cell death and reducing metastatic potential (Bayat Mokhtari, 2017). Furthermore, scientists have suggested that multiscale computational approaches developed to pursue combination anticancer therapies should incorporate alternative strategies shown to be effective against cancer, such as targeting the epigenome, the tumor microenvironment, and even the microbiome (Dry, 2016).

Generating combination drug treatments in precision oncology requires knowledge of drug interactions with the targets modulated by different genetic variants as well as prioritization of variant-related targets according to known interactions with existing drugs (Blucher, 2017). One viable approach encompasses drug repurposing combined with other therapeutics. For instance, a Phase II clinical trial for the treatment of non-squamous non-small-cell lung cancer repurposed itraconazole (an FDA-approved anti-fungal drug with anti-angiogenic activity) in combination with pemetrexed, a chemotherapy drug. Results of the study showed that 67% of the patients on the drug combination were progression-free at three months, compared to 29% in the control arm with pemetrexed alone. The median overall survival was also longer in patients receiving the combination therapy (32 months) versus the control group (8 months) (Rudin, 2013).

The integration and analysis of disparate data to develop predictive drug combination activity has shown signs of success. For instance, Sun et al. (2015) demonstrated that genomic and network characteristics resulted in good performance in predicting synergistic drugs for cancer. The authors confirmed approximately 64% of their predictions for breast cancer through experimental validation and literature research. They also identified that the combination of erlotinib and sorafenib has strong synergy and low toxicity in a relevant tumor model.

Advances in computational approaches coupled with increasing volumes of data offer the possibility to better model and predict the activity profile of drugs relevant to certain targets, which can be immensely valuable for precision oncology applications. A big data analysis of drug targets may provide useful information to highlight potential combinations that exploit the Achilles’ heel of disease-specific pathways (Rastelli, 2015).

**Real-world Evidence**

Randomized controlled trials remain the gold standard for evaluating the safety and efficacy of new drugs. However, their limitations are well recognized (Bothwell, 2016). These limitations are exacerbated in precision medicine, because these trials are often small and provide incomplete insights into those
outcomes that regulators care about the most (e.g., overall survival) (Lewis, 2017). Other methodologies, such as evidence from real-world data sources, are being utilized more and more to make up for data gaps. Real-world data are often generated in observational post-approval studies (e.g., Phase IV). Such studies largely depend on registries and other electronic data, such as EHRs, with the characteristics of big data (Lewis, 2017; Schilsky, 2017).

The evidence derived from the aggregation and analysis of real-world data is commonly referred to as “real-world evidence” (Schilsky, 2017). The quality of the source data that feeds registries and machine learning systems often dictates how useful real-world data will be to generate clinically beneficial information. For instance, certain oncology clinical endpoints, such as response and progression events, are not currently captured as standardized, structured data elements and can only be extracted from clinical notes by manual curation or natural language processing (Schilsky, 2017). However, advancements in natural language processing and machine learning capabilities are improving the extraction, analysis, and reliability of real-world data, some of which is structured (e.g., billing and lab codes, patient history and demographics) and some unstructured (e.g., physician notes, diagnostic reports). Overall, as structured data reporting of additional endpoints (including pathology and images) within EHRs increases, this should facilitate the efficient incorporation of additional data streams into analysis of real-world data (Dangi-Garimella, 2017).

The FDA is also committed to the use of real-world evidence in the context of regulatory decision making. The agency recognizes that randomized clinical trials often have poor generalizability and that treatment decisions based on the median outcome of a trial are not useful for maximizing the potential of precision oncology (Dangi-Garimella, 2017). The FDA’s recently released guidance Use of Real-World Evidence to Support Regulatory Decision Making for Medical Devices confirms its commitment to the use of real-world data (FDA, 2017). Further, speaking at a recent workshop on RWE at the National Academies of Sciences, Engineering, and Medicine, Janet Woodcock (Director of the Center for Drug Evaluation and Research at FDA) stated that the current clinical trial system is broken and is not adequate to address current needs. She also noted that FDA is working on a draft guidance on RWE and a framework for its use and she expects these to be available before 2021.

Looking Ahead: Precision Oncology Trials
Approaches to conducting precision oncology trials will continue to evolve, and this evolution will require data and technologies in the clinical development process to effectively deal with the dichotomy of patient scarcity and abundance of disparate data. Innovations in precision oncology trials are also enabling drug development by non-traditional sponsors such as the Leukemia & Lymphoma Society (LLS) which is leading the Beat AML® Master Trial. LSS is working with Medidata on this groundbreaking clinical trial to test novel targeted therapies for patients with acute myeloid leukemia (AML).

As large datasets are used to cluster patients into ever more precise subsets, investigators will have to measure patients on several dimensions, ranging from genotype to phenotype (e.g., genotype, laboratory data, digital biomarkers, sensor data, behavioral data, histological images, photos, and point-of-care notes). By capturing a wider variety of nontraditional data derived as close to the source as possible, big data offers opportunities for precision oncology (Beckmann, 2016; Dinov, 2016). This requires the adoption of clinical development technologies that can facilitate precision oncology trials not only by enabling the efficient collection, aggregation, and integration of data but by empowering the exploratory and iterative processes that drive the precision oncology approach via powerful analytics.

For instance, big data approaches that integrate disparate data sources will be the best positioned to leverage information that facilitates the development of novel targeted therapies and more efficiently help with drug repurposing and identification of novel drug combinations. With an adequate infrastructure in place to ingest, standardize, and analyze large volumes of disparate data, precision oncology applications can be optimized using specific approaches and technology.

The first step is efficient study planning:

- Intensive pre-protocol research to build multiple hypotheses to be tested, depending on the overall drug repurposing/combination therapy strategy
- Writing of protocols in a balanced way to focus on a narrow set of objectives that may flexibly yield several outcomes of interest
- Necessary considerations relating to where regulatory bodies like the FDA will draw the line regarding exploratory hypothesis testing (too many hypotheses can be viewed as unfavorable and lacking a defined research objective)
- Utilization of innovative clinical trial designs, such as adaptive trials or single-arm trials leveraging SCAs

Once the study trial design has been finalized, site selection and patient recruitment is initiated. This step must incorporate a well-defined strategy that adequately addresses patient scarcity, such as by using specific biomarkers that match the study protocol. Importantly, advanced analytics on historical site performance can be used to recognize sites with a higher probability for identifying and recruiting relevant patients (e.g., the OPAL site selection described earlier). Synthetic control arm technology can also be used to reduce sample sizes by 50% while maintaining a sufficiently powered study.
“Today’s gold standard for clinical trials is the prospective enrollment of a 1-to-1 ratio of treatment and control patients. However, emerging clinical development platforms will increasingly enable the future gold standard of a N-to-1 ratio of treatment and control patients.” - Glen de Vries, president of Medidata.

That is, for every prospectively enrolled patient on an experimental therapy, there will be 1 prospectively enrolled control patient, 1 synthetic control patient, and 1 real-world comparator. This type of emerging collaborative platform will reduce the cost and ethical burden associated with control/placebo arms, while increasing the probability of a successful trial and expediting time-to-market.

Upon finalization of the study and recruitment plan, the data collection, management, and analysis procedures must be in place to properly interpret the data. Advanced analytic tools like Centralized Statistical Analytics can be utilized to sort patient responses. Furthermore, the Adaptive Randomization and Trial Supply Management (RTSM) tool can be used to modify treatments per recruitment in real-time as data are collected.

Precision oncology trials rely heavily on clinicians and researchers to think about emerging data in new ways and develop innovative strategies to fully leverage the massive body of data generated. After the end of the study, advanced analytics, such as Clinical Trial Genomics, can uncover biomarkers of response or indicative of metastatic progression, new subgroups of responsive patients, new diagnostic criteria or risk factors, novel combinations of drugs, or repurposed treatments. This process can result in revised or even completely novel studies with increasingly focused hypotheses to be tested.

Precision oncology is a journey that demands flexible and iterative processes. As a specific precision oncology journey matures, investigators can expect that future iterations will involve additional rounds of testing for new biomarkers, building new combination therapies, and evaluating drug repurposing strategies. The cyclical nature of this approach can help accelerate precision oncology efforts.

Clinical development technologies and the analysis of a wealth of disparate data can help investigators overcome some of the common pitfalls associated with precision oncology drug development. Novel biomarker data integrated into innovative oncology trial designs, coupled with real-world evidence and other disparate data, will certainly continue to enhance the success of precision oncology trials for the benefit of patients.

**Summary**

The field of oncology has been leading the precision medicine revolution, and precision oncology treatments have provided several astonishing treatments that have improved outcomes for many patients. As this field continues to mature and evolve, it will require increasingly sophisticated technologies to deal with the dichotomy facing precision oncology drug developers: patient scarcity and abundance of disparate data.

Dissection of this dichotomy will require the adoption of clinical development technologies that enable the efficient collection, aggregation, and integration of data, in addition to advanced analytics that uncover relationships in the data that would not have been realized by human analysis alone. These technologies harness a variety of disparate data sources at richer and greater volumes, and help with optimal site selection, patient recruitment, and innovative trial designs, such as those utilizing synthetic control arms.

A clinical development platform that allows for an iterative research process widens the possibility of achieving success in precision oncology. Engaging in early consultation with an experienced partner can help avoid common pitfalls and facilitate the right platform for your program.

**References**


