Precision Oncology Trials: A Look Ahead

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Executive Summary

Pharmaceutical and biotechnology companies are increasingly incorporating patient genetic and genomic information in their clinical development programs. One of the goals of this endeavor is to introduce the ability to identify biomarkers that can be used to target specific subsets of patients with the most effective treatments. However, this strategy can frustrate drug sponsors because many cancer mutations are extraordinarily rare which means that a potential patient pool can erode very quickly making it difficult to enroll the right patient population in a timely fashion. Exacerbating the frustration of drug sponsors is the notion of how to deal with the increasing and constant stream of newly emerging data (often from disparate sources) arising from basic and clinical research that may be relevant to a clinical development program. Given the current poor predictive ability when it comes to the correlation between biomarker status and relevant clinical response rate, incorporating additional relevant data streams will likely generate insights and efficiencies that were not possible even a few years ago.

Clinical development technologies are a powerful partner when it comes to complex precision oncology trials. As these trials continue to evolve and increase in complexity, this evolution will require clinical development technologies with advanced analytics that are driven by massive computing power. These technologies are helping sponsors overcomes challenges related to the dichotomy discussed above — *patient scarcity* versus *abundance of disparate data*. This paper examines how clinical development technologies and analysis of a wealth of disparate data can help investigators overcome some of the common pitfalls associated with precision oncology drug development.

Introduction

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 success of precision oncology relies on the development of validated biomarkers that can be targeted with molecular therapies (Collins, 2015; Woodcock, 2017; NCI, 2017). With greater accessibility to genomic testing and validated biomarkers, oncology clinical research continues to increase in complexity. Scientists regularly uncover new challenges related to tumor heterogeneity, adaptation, evolution, and drug resistance, as well as previously unrecognized interactions between drugs and the human proteome (i.e. the entire set of proteins expressed by a genome) (Antolin, 2016; Blucher, 2017). The rise of precision oncology has facilitated the approval of several new drugs including 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.

> **"The large differences in Phase II and III transition success rates are quite convincing, quantitatively, of what many drug developers have long argued anecdotally — enrichment of patient enrollment at the molecular level is a more successful strategy than heterogeneous enrollment."**
>
> Thomas, 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):

1. **Precision medicine and immunotherapy** have experienced massive research investments further in the direction of precision medicine with meaningful improvements in survival for patients with traditionally challenging diseases.
2. **Real-world evidence and data sharing** initiatives are more often being facilitated by various stakeholders.
3. **Practice transformation** is ongoing, sparked by innovative payment models that promote and incentivize high-quality cancer care. Indeed, value-based systems can be expected to expand.

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) (Kolata, 2017). In addition, there are record numbers of oncology clinical trials (there are an estimated 1,000+ immunotherapy clinical trials currently underway), meaning that sponsors are competing for patients from the same limited pool of potential recruits.

Furthermore, increasing numbers of disparate data streams are generating large volumes of data that can potentially better 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.

This dichotomy — *patient scarcity versus abundance of disparate data* — 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.

This is where optimized clinical development technologies come into play. These technologies are key to supporting precision oncology trials since they harness a variety of disparate data sources at richer and greater volumes, and 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 intention of this paper is to provide a high-level discussion of how clinical development technologies can help drug sponsors address the dichotomy of patient scarcity versus an abundance of disparate data, as well as a look ahead for precision oncology trials.

> **"Technical advances including monitoring devices with direct data transmissions into large, growing databases and analysis of disparate data will allow to create increasingly precise, better and relevant historical controls for decision making. The integration of validated predictive biomarkers with other data streams is essential as it will influence novel designs and enable the success of precision oncology trials."**
>
> Reinhard Von Roemeling, Former Senior Vice President of Clinical Development and Global Oncology Head at EMD Serono

Patient Scarcity and Abundance of Disparate Data

Clinical development technologies are increasingly being utilized by drug sponsors to more efficiently recruit patients and seamlessly deal with increasing numbers of disparate data streams. The following sections provide a short discussion of the two key challenges facing drug sponsors: *patient scarcity and abundance of disparate data*, followed by solutions offered by Medidata that can help sponsors overcome these well-recognized challenges.

Patient Scarcity

The increasingly targeted nature of precision drugs coupled with an escalating number of oncology clinical trials has created a patient recruitment challenge for precision oncology (Kolata, 2017). While recent developments in **targeted therapies** and **immunotherapies** have delivered significant benefit to cancer patients, these two areas exemplify the patient scarcity challenge.

TARGETED THERAPIES

The inclusion of genetic and genomic information in clinical development programs has been a key driver for precision oncology given that many cancer mutations are extraordinarily rare (Rehm, 2017; Peterson, 2017; Conley, 2016; Tuna, 2012). However, rare mutations can quickly erode a potential patient pool as demonstrated in a study by Kavuri et al. (2015).

In the study, the investigators evaluated the impact of *HER2* mutations in colorectal cancer (these mutations have been identified in only ~7% of patients). 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).

IMMUNO-ONCOLOGY THERAPIES

The basic premise underlying immuno-oncology therapies is that the immune system can destroy tumor cells *if it can detect them*. 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.

> **"The many targeted cancer therapies in development today can save patients' lives, but only if we improve clinical trials so they reach the patients who can benefit from them. Optimizing trial design, site selection and patient recruitment increases the effectiveness of clinical trials and improves patients' access to new treatments."**
>
> Ken Tarkoff, CEO, Syapse

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). It is undisputed that biomarkers are the cornerstone of precision oncology drug development (Woodcock, 2017). A recent study undertaken by biotech's largest trade organization found that oncology drugs have the lowest likelihood of approval (LOA) from Phase I (5.1% vs. 11.9% for all indications outside of oncology). However, the use of selection biomarkers raised 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).

Figure: Phase success rates and LOA from Phase I for oncology vs. non-oncology indications (Redrawn from Thomas, 2016)

**Probability of Success
Oncology vs. Non-Oncology**
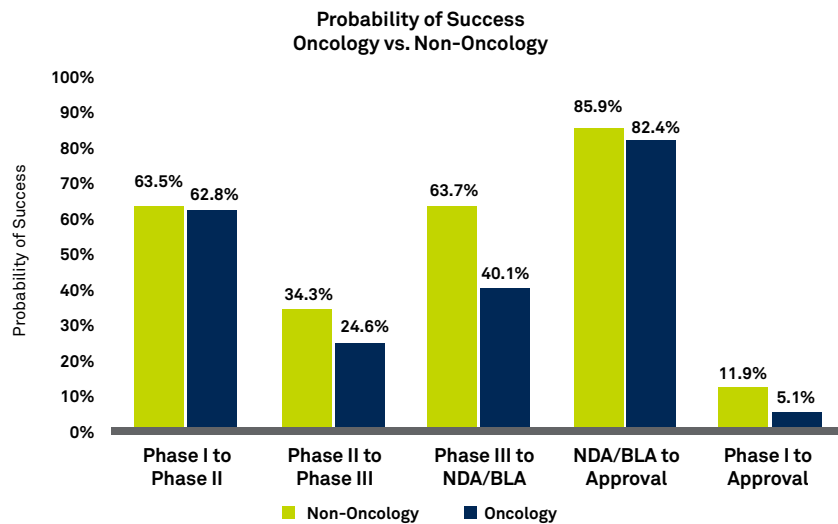
The integration of increasingly reliable biomarker data with other data streams may prove to be an invaluable approach for developing novel precision oncology therapies. The following sections describe three areas that may benefit from the use of disparate data: drug repurposing, combination therapies, and real-world evidence.

DRUG REPURPOSING

The repurposing of existing drugs for new indications is a growing area of interest in the development of oncology drugs and it is a recognized strategy that has had some successes (Bayat Mokhtari, 2017; Oprea, 2012; Azvolinsky, 2017; Coyle, 2016; Sun, 2016; Nosengo, 2016). 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; Sagers, 2016; Xu, 2015).

COMBINATION THERAPIES

Combination drug treatment is an important paradigm in cancer therapy since the use of multiple therapies can reduce the likelihood of drug resistance and can produce superior anticancer benefits (Bayat Mokhtari, 2017; Sun, 2015). 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). Further, 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 (Rastelli, 2015; Dry, 2016).

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 precision medicine 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. Rapid 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; Schilsky, 2017).

Further, the FDA is also committed to the use of real-world evidence in the context of regulatory decision making. Janet Woodcock (Director of the Center for Drug Evaluation and Research at FDA) recently stated that the agency is working on a draft guidance on real-world evidence and a framework for its use which is expected to be available before 2021.

"Large, high quality databases allow formation of historical control cohorts that match the eligibility criteria of single arm trials and provide critical endpoint / outcome data after standard treatment for go/no-go decisions or even support of regulatory submissions."

Reinhard Von Roemeling, *Former Senior Vice President of Clinical Development and Global Oncology Head at EMD Serono*

Looking Ahead: Precision Oncology Trials

Precision oncology approaches will continue to mature in the coming years 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 Synthetic Control Arms (i.e., carefully matched controls created with historical patient-level clinical trials data).

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. For instance, Operational Performance Analytics (OPAL) evaluates the clinical research study and historical site performance 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) and to recognize sites with a higher probability for identifying and recruiting relevant patients. Synthetic control arm technology could be used to augment a randomized control and reduce the number of patients assigned to the control arm 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, Co-Founder of Medidata

That is, in the future, for every prospectively enrolled patient on an experimental therapy, there will be < 1 prospectively enrolled control patient since controls may be augmented by synthetic control patients, and real-world evidence. 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. 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).

> **"Synthetic control arms utilize advanced matching algorithms that enable better estimation of treatment effect from a single-arm trial, and therefore provide better prediction of subsequent later-phase randomized clinical trials. Thus, adoption of synthetic control arms will decrease clinical development failure rates, estimated to be close to 90% from Phase I to regulatory approval. In the future, synthetic control arms will also enhance understanding of disease subgroups, aid in the selection of new endpoints, and reduce the number of patients in control arms with futile standard-of-care or placebo treatments."**
>
> David Lee, Chief Data Officer at Medidata, as Quoted in Preston, 2017

Upon finalization of the study and recruitment plan, the data collection, management, and analysis procedures must be in place to properly interpret the data. RaveX is a flexible and adaptive solution for capturing, managing and reporting patient data, including unified electronic data capture, clinical data management system (CDMS), and lab administration features. With RaveX sponsors can make study changes in real-time — including adaptive trials, protocol amendments and updated requirements easily. 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 population *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.

> **"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

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

Akbay EA, Koyama S, Carretero J, Altabef A, Tchaicha JH, Christensen CL, Mikse OR, Cherniack AD, Beauchamp EM, Pugh TJ, Wilkerson MD, Fecci PE, Butaney M, Reibel JB, Soucheray M, Cohoon TJ, Janne PA, Meyerson M, Hayes DN, Shapiro GI, Shimamura T, Sholl LM, Rodig SJ, Freeman GJ, Hammerman PS, Dranoff G, Wong KK. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov. 2013 Dec;3(12):1355-63.

Anighoro A, Bajorath J, Rastelli G. Polypharmacology: Challenges and Opportunities in Drug Discovery. *J. Med. Chem.* 2014, 57 (19), pp 7874–7887.

Antolin AA, Workman P, Mestres J, Al-Lazikani B. Polypharmacology in Precision Oncology: Current Applications and Future Prospects. Curr Pharm Des. 2016; 22(46):6935-6945.

ASCO (2017). The State of Cancer Care in America, 2017: A Report by the American Society of Clinical Oncology. Journal of Oncology Practice 2017 13:4, e353-e394

Azvolinsky, A. Repurposing Existing Drugs for New Indications. The Scientist. [Online] Available at: http://www.the-scientist. com/?articles.view/articleNo/47744/title/Repurposing-Existing-Drugs-for-New-Indications. [Accessed 9/21/2017].

Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, Yeger H. Combination therapy in combating cancer. Oncotarget. 2017 Jun 6;8(23):38022-38043.

Beckmann, J. S., & Lew, D. (2016). Reconciling evidence-based medicine and precision medicine in the era of big data: challenges and opportunities. *Genome Medicine,* 8, 134.

Berry, D.A., M. Elashoff, S. Blotner, R. Davi, P. Beineke, M. Chandler, D.S. Lee, L.C. Chen, and S. Sarkar. 2017. Creating a synthetic control arm from previous clinical trials: Application to establishing early end points as indicators of overall survival in acute myeloid leukemia (AML). *Jco*. 35:7021-7021.

Blucher AS, Choonoo G, Kulesz-Martin M, Wu G, McWeeney SK. Evidence-Based Precision Oncology with the Cancer Targetome. Trends Pharmacol Sci. 2017 Sep 27. pii: S0165-6147(17)30166-9.

Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard — Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81.

Chen B, Butte AJ. Leveraging big data to transform target selection and drug discovery. Clin Pharmacol Ther. 2016 Mar;99(3):285-97.

Collins FS, Varmus H. A new initiative on precision medicine. The New England journal of medicine. 2015;372(9):793–5

Conley B, Sorg BS, Tricoli JV. Implications and opportunities of precision medicine in rare malignancies. *Expert Opinion on Orphan Drugs*. 4(9), 2016.

Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for cancer: a systematic review and meta-analysis. Ann Oncol. 2016 Dec;27(12):2184-2195.

Dangi-Garimella, S. Physician, Regulatory, and Payer Perspectives on the Value of Real-World Data. The American Journal of Managed Care® website. Available online: http://www.ajmc.com/journals/evidence-based-oncology/2017/july-2017/physician-regulatory-and-payer-perspectives-on-the-value-of-real-world-data. Published July 20, 2017. Accessed 10/8/2017

Dinov, I. D. (2016). Methodological challenges and analytic opportunities for modeling and interpreting Big Healthcare Data. *GigaScience*, 5(1), 12.

Dry JR, Yang M, Saez-Rodriguez J. Looking beyond the cancer cell for effective drug combinations. Genome Med. 2016 Nov 25;8(1):125.

FDA (2017). Two Recent Scientific Advances Underscore an Encouraging Future for Precision Medicine at FDA. FDA Voice. [Online] Available at: https://blogs.fda.gov/fdavoice/index.php/2017/07/two-recent-scientific-advances-underscore-an-encouraging-future-for-precision-medicine-at-fda/ [Accessed October 9, 2017].

Gajewski TF, Fuertes M, Spaapen R, Zheng Y, Kline J. Molecular profiling to identify relevant immune resistance mechanisms in the tumor microenvironment. Curr Opin Immunol. 2011;23(2):286-292.

Hoos A. Development of immuno-oncology drugs — from CTLA4 to PD1 to the next generations. Nat Rev Drug Discov. 2016 Apr;15(4):235-47.

Iwai, Y., Hamanishi, J., Chamoto, K., & Honjo, T. (2017). Cancer immunotherapies targeting the PD-1 signaling pathway. *Journal of biomedical science,* 24(1), 26.

Kavuri SM, Jain N, Galimi F, Cottino F, Leto SM, Migliardi G, Searleman AC, Shen W, Monsey J, Trusolino L, Jacobs SA, Bertotti A, Bose R. HER2 activating mutations are targets for colorectal cancer treatment. Cancer Discov. 2015 Aug;5(8):832-41.
Kolata G. 2017. A Cancer Conundrum: Too Many Drug Trials, Too Few Patients. The New York Times. https://www.nytimes.com/2017/08/12/health/cancer-drug-trials-encounter-a-problem-too-few-patients.html. Accessed 9/21/2017

Lewis R.R.J., Kerridge I., Lipworth, W. Use of Real-World Data for the Research, Development, and Evaluation of Oncology Precision Medicines. *JCO Precision Oncology* 2017 :1, 1-11

Mehnert, J. M., Monjazeb, A. M., Beerthuijzen, J. M., Collyar, D., Rubinstein, L., & Harris, L. N. The challenge for development of valuable immuno-oncology biomarkers. Clin Cancer Res September 2017; 23 (17): 4970-4979.

NCI (2017). Targeted Cancer Therapies. [Online] Available at: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet [Accessed October 9, 2017].

Nosengo N. Can you teach old drugs new tricks? Nature. 2016 Jun 16;534(7607):314-6.

Oprea TI & Mestres J. Drug Repurposing: Far Beyond New Targets for Old Drugs. *AAPS J*. 2012 Dec; 14(4): 759–763.

Peterson TA, Gauran IIM, Park J, Park D, Kann MG. Oncodomains: A protein domain-centric framework for analyzing rare variants in tumor samples. PLoS Comput Biol. 2017 Apr 20;13(4):e1005428.

Preston J. Medidata wants to help control your single-arm clinical trials. MedCity News. https://medcitynews.com/2017/05/medidata-control-arm-clinical-trial. Accessed 10/7/2017.

Rastelli G & Pinzi L. Computational polypharmacology comes of age. *Front Pharmacol*. 2015 Jul 28;6:157. doi: 10.3389/fphar.2015.00157. eCollection 2015.

Rehm HL. Evolving health care through personal genomics. Nat Rev Genet. 2017 Apr;18(4):259-267.

Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in nonsmall cell lung cancer. Science. 2015;348(6230):124-128.

Sagers, J. (2016) Re-Engineering Cures for the Big Data Age: Precision Medicine and Computational Drug Repositioning. [Online] Available at: http://sitn.hms.harvard.edu/flash/2016/re-engineering-cures-big-data-age-precision-medicine-computational-drug-repositioning/ [Accessed October 9, 2017].

Schilsky R. Finding the Evidence in Real-World Evidence: Moving from Data to Information to Knowledge, In Journal of the American College of Surgeons, Volume 224, Issue 1, 2017, Pages 1-7.

Shin, S. H., Bode, A. M., & Dong, Z. Addressing the challenges of applying precision oncology. *npj Precision Oncology*. 2017 1(1), 28.

Sleeman, J & Steeg PS. Cancer metastasis as a therapeutic target. *Eur J Cancer.* 2010 May;46(7): 1177-80.

Steeg PS. Targeting metastasis. Nature Reviews Cancer. 2016 16, 201–218.

Stone J. How Can We Encourage Participation in Clinical Trials? Forbes Pharma & Healthcare. https://www.forbes.com/sites/judystone/2015/01/06/how-can-we-encourage-participation-in-clinical-trials/#4c150b964d0c. Accessed 9/21/2017.

Sun Y, Sheng Z, Ma C, Tang K, Zhu R, Wu Z, Shen R, Feng J, Wu D, Huang D, Huang D, Fei J, Liu Q, Cao Z. Combining genomic and network characteristics for extended capability in predicting synergistic drugs for cancer. Nat Commun. 2015 Sep 28;6:8481.

Sun W, Sanderson P, Zheng W. Drug combination therapy increases successful drug repositioning. *Drug Discov Today*. 2016 Jul; 21(7): 1189–1195.

Thomas, D. W., Burns, J., Audette, J., Carrol, A., Dow-Hygelund, C., & Hay, M. (2016). Clinical development success rates 2006-2015. *San Diego: Biomedtracker/Washington, DC: BIO/Bend: Amplion*.

Tuna M., Amos C.I. (2012). Activating Mutations and Targeted Therapy in Cancer, Mutations in Human Genetic Disease, Prof. David Cooper (Ed.), InTech, DOI: 10.5772/48701. Available from: https://www.intechopen.com/books/mutations-in-human-genetic-disease/activating-mutations-and-targeted-therapy-in-cancer

Woodcock J & LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med*. 2017; 377:62-70; DOI: 10.1056/NEJMra1510062.

Xu H, Aldrich MC, Chen Q, Liu H, Peterson NB, Dai Q, Levy M, Shah A, Han X, Ruan X, Jiang M, Li Y, Julien JS, Warner J, Friedman C, Roden DM, Denny JC. Validating drug repurposing signals using electronic health records: a case study of metformin associated with reduced cancer mortality. J Am Med Inform Assoc. 2015 Jan;22(1):179-91.