A cancer diagnosis is a life-changing event. For advanced cancer in particular, standard of care treatments have limited impact on long term patient survival. Precision Medicine is transforming cancer care for patients with early stage and advanced cancers alike. Next Generation Sequencing and other molecular tests are leading to the discovery and approval of a growing number of effective targeted cancer therapies that are based on the molecular characteristics of tumors.

2015 was a banner year for advancing the availability of new therapeutic options for cancer patients. The FDA approved 14 new oncology drugs, up from 9 approvals in 2014. In addition, 13 new indications or formulations were added to previously FDA approved therapies.

Many of these new drugs are targeted therapies directed at the tumor of patients identified to have particular molecular alterations. There is a growing amount of data demonstrating improved therapeutic response when patients are matched to targeted therapies based on their molecular profile. With this mounting validation and physician and consumer awareness, the utilization of NGS testing is increasing in both the academic and community oncology communities, and many hospital networks are launching precision medicine programs to provide greater access to molecular profiling to their patients with cancer.

While the number of approved targeted therapies has rapidly grown, FDA approved targeted therapies address the treatment needs of a limited number of patients, and clinical trials are often the best way for a patient to get access to a targeted therapy. There are over 3000 clinical trials for cancer therapies in the US alone. Over 2015, many new therapies have received breakthrough therapy designation based on the results of early stage trials.

Thus, clinical trials are rapidly becoming the most effective and rapid way for patients to access novel therapies that may be their “best” treatment option based on their molecular profile.

This has led to a shift in clinical trial paradigm. Historically, patients were matched to clinical trials based on the organ of origin and histology of their cancer without consideration of molecular alterations that may be present in their tumors. However, a growing number of studies have demonstrated that using molecular markers to stratify patients into appropriate clinical trials can significantly improve success rates of trials.
Despite these phenomenal changes in clinical trial paradigm and growing awareness of the potential benefit to patients in pursuing relevant clinical trials, significant barriers to clinical trial enrollment remain. Still, only 3–7% of oncology patients in the US participate in clinical trials. An analysis of more than 500 NCI Cancer Therapy Evaluation Program (CTEP) trials by Steven Cheng revealed that 40 percent of trials failed to achieve minimum patient enrollment, and more than three of five phase III trials failed to do so.

**Barriers to Participation**

**The Patient Perspective:**

One of the main barriers to clinical trial participation is that patients are unaware of the availability of trials for their cancer. In 2013, a national poll through Research! America found that 72% of Americans would be likely to participate in a clinical trial if it was recommended by their doctor, but only 22% say a doctor or other health care provider has discussed clinical trials. The majority of patients who hear about trials do so through the internet and less than a quarter did through their physician. Patients and their families often receive limited guidance from their physicians about relevant trials and need to sift through hundreds of trials trying to find the trial that would be the best match for them. Thus, patients often turn to online resources to search for a trial. These online tools, however, have an overwhelming amount of information on the trials that may be out of date, incomplete or too complex for most patients and families to navigate alone. With the rise of molecular medicine in oncology, in particular, many of the trials are targeted therapy trials with complicated scientific requirements and inclusion/exclusion criteria based on a patient’s tumor molecular profile. Patients may lack the scientific background required to understand the significant potential advantages of receiving a targeted therapy based on their molecular profile, the detailed exclusion and inclusion criteria, and the new trial paradigms designed to assess therapeutic efficacy in small subgroups of patients.

In addition, other studies have shown that fear or lack of understanding is a significant barrier. Patients are concerned with potential toxicity from a novel therapeutic, receiving a drug in phase I when often these drugs are well studied in other cancer types, or with the possibility of receiving a placebo even though “best” standard of care is the comparator arm. In addition, the most clinically relevant trials may not be located near a patient’s home which can create additional financial, physical and personal barriers to enrollment. Despite the 2014 Affordable Care Act (ACA) which requires that all insurance providers cover the cost of clinical trial participation for cancer patients, there remains inconsistent coverage and the risk of incurring significant cost continues to be a barrier to patient enrollment in clinical trials.

**The Provider Perspective**

Oncologists are on the front lines in supporting cancer patients and their loved ones through diagnosis and treatment, yet over the years they have greater barriers to overcome as they advocate for the patients in their care. Many physicians, even at major academic medical centers, often do not feel confident in their ability to interpret patients’ genomic information. This is not getting easier. The science is progressing rapidly and every day new data emerge on potential new targets for therapies, novel resistance mechanisms, new compounds entering the clinic, and new molecular tests become available. Hospital information systems providing clinical trial information are very fragmented and information on particular trials is often sequestered in an institution by cancer type and phase.

**Top Sources of Clinical Trial Information:**

![Figure 1](image-url)
Depending on the site’s investment in clinical research technology, they may not have a centralized clinical trial management system (CTMS), which makes larger institutions with oncology care split between multiple departments, at a disadvantage of even knowing which clinical trials are currently enrolling at their site.

Driving Change

**Empowering the Physician and Patient:** Despite the many barriers for oncology patients and their physicians, the advent of these new technologies and therapies that are transforming outcomes in care are also resulting in incredible innovation to enable better access for patients and physicians.

Physicians need rapid access to the clinical and scientific evidence that is the critical link between each patient’s molecular data generated by Next Generation Sequencing and other molecular tests and the appropriate therapeutic options. The molecular test results of each patient’s tumor profile must be analyzed to assess the molecular effect of each individual’s clinically relevant alterations as well as the combination of alterations in the context of each patient’s cancer subtype to determine the link to possible relevant therapeutic strategies. As the complexity of the molecular data continues to grow and our understanding of the data evolves, so too does the complexity of clinical trial design.

Over the past few years, two new trial methodologies have emerged in order to address this need:

1) Basket or Bucket trials
2) Umbrella trials

In both these methods, patients are matched based on their biomarker status. The Basket trials such as NCI-Match, match patients to drugs in a variety of tumor types testing a single drug on a single mutation. Whereas,
Umbrella trials, like BATTLE, are designed to assess the effect of different drugs on different mutations in a single cancer type. In addition, adaptive trial designs enable researchers to amend the trial protocol based on emerging data at pre-specified time points during the trial. Furthermore, ASCO has launched TAPUR which is designed to assess the efficacy of multiple therapies approved for other indications, “off-label” drugs, by matching patients to the different therapies based on the molecular results of each patient’s tumor sequencing.

These changes in trial design further necessitate new ways of connecting patients and physicians to the most relevant clinical trials based on a detailed analysis of the results of NGS testing.

To find relevant trials for a cancer patient, labs are partnering with companies like N-of-One to get access to detailed clinical interpretation of each patient’s molecular profile. This requires:

- Gene, variant and disease-specific analysis of each patient’s tumor profile which is critical for making the right trial match.
- Multi-variant analysis to understand drug resistance, drug sensitivity and the potential for combination therapies.
- Trials need to be chosen based on the molecular features of the drug and each arm of the trial – “Molecular Eligibility™”.

In addition,

- Clinical Trial Matching can be enhanced when patients are also matched based on their location as they prefer generally to enroll in trials at the institutions where they are being treated—otherwise, at a hospital that is close to home.
- The physician needs easy access to the clinical and scientific evidence supporting the particular trials at the point of care to enable efficient discussion with the patient about relevant trials.

Armed with the evidence of the implications of a patient’s molecular profile on drug sensitivity, drug resistance and combination therapies and knowledge of the molecular features of the drug and each arm of the trial, physicians can more readily match their patients to relevant targeted therapy trials.
For Example, Intermountain Healthcare conducted a study comparing cancer treatment decisions with and without utilization of molecular data and clinical interpretation from N-of-One. They demonstrated that treatment changed to targeted therapy in 62% of cases where molecular testing and N-of-One interpretation were available. In addition, in a small retrospective cohort, they demonstrated that progression free survival was 22.9 weeks for precision therapy cohort compared to 12.0 weeks for standard of care therapy cohort with slight cost savings.55

Quintiles, US Oncology and N-of-One conducted a pilot study in 51 patients with advanced colorectal cancer to demonstrate that molecular testing with expert clinical interpretation could impact clinical trial enrollment rates. Results showed that the report had a significant influence on physician referral to clinical trials as 35% of patients were referred to a trial.26

Even with the best knowledge of relevant trials, however, additional services may still be required to close the loop for the patient and physician on connecting with trial sites. Access to nurses who have the skills to answer questions on the trials, and who can provide clinical trial pre-enrollment navigation services, can potentially significantly improve patient recruitment and enrollment.

**Connections from Sponsors and CROs**

Pharma sponsors and CROs have begun to recognize the intensity of the barriers for oncology patient participation into clinical trials and have begun to drive change in how they engage with research sites and patients.

Novartis has created their Signature pilot program, where participating US based research sites can access modular Phase II studies for a particular patient with an investigational targeted therapy. They have combined these studies with a method for rapid opening at the requesting site, with metrics stating site opening takes approximately 3 weeks. This timeline is clinically relevant for a patient to wait for access to a novel molecule, especially when they have run out of treatment options. The modular approach to the regulatory documents requires site research staff to accept the terms defined by Novartis, however, upon the investment of time to start the trial, a known patient will be offered participation.27

Quintiles has launched their Precision Enrollment services, where a network of 80 oncology sites within the US will be participating. Patients will be pre-identified through biomarker and EHR analysis and the participating sites can request the appropriate clinical trial to be opened at their site within 21 days. In contrast to the modular system used in the Novartis Signature pilot program, Quintiles Precision Enrollment (QPE) requires sites pre-negotiate agreements and be pre-qualified as part of the process to join.28

With both Signature and QPE, Novartis and Quintiles are taking aim to solve the critical challenge of getting the right drug to the right patient quickly. The speed of 21 days to open a clinical trial, in contrast to the industry best in class metric of 90 days, requires fundamentally changing how we complete the regulatory and contractual requirements for opening a clinical trial.

In contrast to the change of critical path employed by Signature or QPE, 20 different pharmaceutical companies have partnered to form the non-profit TransCelerate Biopharma, Inc. with the sole goal of harmonizing clinical trials processes. With harmonization, they expect to dramatically reduce site administrative burden and increase the speed of running clinical trials. This time savings for sites can be used to increase the number of trials opened, increasing patient access, and allow more site staff to focus on direct patient care.29

**A Changing Landscape in Oncology Research**

Along with the leadership from drug developers and CRO partners, we are seeing rapid changes and investments to ease barriers to patient participation in oncology clinical trials coming from the US government and non-profits such as the American Society of Cancer Research (ASCO). Vice President Biden is leading the Moonshot program, where the US will be investing over $1 billion in cancer research, inclusive of removing regulatory barriers for approval of breakthrough therapies, allowing for better ease of medical data sharing to drive faster insights and supporting clinical trial access to patients in the community setting. By changing the regulatory environment, the Moonshot program will have the ability to speed promising drugs to market and drive more effective go no-go decision making in drug development. Patients benefit when the right drugs get to market quickly, increasing access and reimbursement to medicines that provide patient value.30

Recently launched by the National Cancer Institute (NCI), the PRE-ACT patient resources are available online for free for patients and researchers to better educate patients regarding participation in oncology clinical trials. Reported in the Journal of Clinical Oncology, researchers were able to show 21% of oncology patients (N=1,255) enrolled into a clinical trial.
within 6 months of receiving targeted information regarding their questions and barriers on clinical trial participation. Patients received specific targeted videos using ‘Preparatory Education About Clinical Trials (PRE-ACT)’ or NCI developed text based education. Because patients received this information prior to their initial oncologist visit, the researchers were assessing how early educational intervention can support patient understanding and openness to clinical trials as a potential treatment option for their cancer.35

In 2012, ASCO released its vision for year 2030 to drive fundamental change and improve oncology patient treatment outcomes. They have remained focused on this vision with the launch of CancerLinQ, which aggregates volumes of medical records to allow physicians and researchers to gain insights on treatment decisions, outcomes and value for patients.36

It is a phenomenal time in the evolution of treatment in oncology. The opportunity to personalize the treatment of every patient based on the biology of their tumor is becoming a reality. Novel therapies are beginning to transform cancer care. Evidence is growing for measuring improved disease response when patients are matched to targeted therapies based on their molecular profile. There has been growing utilization of NGS testing and other molecular tests by oncologists in academic and community settings as part of standard of care. Government and Industry are coming together to provide new ways of connecting patients and physicians to relevant clinical trials based on both molecular and health information. With all eyes focused on increasing patient access to novel treatments, we can collectively break down the barriers. The faster we can open clinical trials, the faster we can support physicians with decision making, the faster we can connect the right patient with the right clinical trial option, the faster we can get regulatory approval, the closer we will be to a cure.

These are challenges we must solve as an industry—we owe this to the patients we serve.

Jennifer Carter MD, MPH Chief Medical Officer and Founder, founded N-of-One in 2008 and currently serves as Chief Medical Officer. A board-certified physician and entrepreneur, Dr. Carter has more than 20 years of experience evaluating existing and emerging markets, new medical technologies and early-stage companies in the health care field. In establishing N-of-One, Dr. Carter brought to the enterprise extensive experience analyzing market opportunities, creating services to improve health care delivery, and identifying business synergies. She also has experience in business analysis and planning for new technologies in health care.

Prior to launching N-of-One, Dr. Carter was a board certified physician. She received an M.D. from Harvard Medical School and an M.P.H. from The Harvard School of Public Health. Dr. Carter has B.S. degrees in Biochemistry and Biophysics from Yale University.

Jennifer Cubino, MA, CCRA, has worked in clinical research for 13 years and has held roles in strategy, innovation, site alliance management, Precision Medicine, operations, clinical trial management and monitoring. In her role at Quintiles she ensures seamless oncology portfolio delivery for large pharma customers. She provides strategic oversight and planning to project teams in developing biomarker, operational, site and patient recruitment strategies and effective risk mitigation. Her therapeutic expertise includes: oncology, infectious disease, respiratory and psychiatric studies in Phases I-IV. She is experienced in creating solutions for development of Biomarker targeted molecules and CDx strategies cross-therapeutically. Ms. Cubino was an appointed member of the Tufts Medical Center IRB for seven years and completed her Bachelor of Science at Cornell University, College of Agriculture and Life Sciences and Master of Arts in Clinical Research at Boston University, College of Medicine.

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