

Precision Medicine Clinical Trials in Oncology

Symposium Proceedings

November 8-10, 2017

Grand Hyatt, Dallas Fort Worth

Sponsored by Research Advocacy Network



Executive Summary

The Precision Medicine Clinical Trials in Oncology Symposium was designed to help patient advocates who are in decision making roles learn more about the current state of precision medicine in oncology and to gather input on the design of future precision medicine trials.

Key Points for Advocates

- Patients need to know that not all genomic test results will show actionable mutations.
- The healthcare team needs to use consistent language and terms that patients can understand.
- Patients need expanded access to tumor profiling.
- Site resources are an important issue.
- Trials often have narrow eligibility requirements, and even patients with actionable mutations may be denied entry.
- The small size of precision medicine trials precludes influence on clinical practice.

Key Points from Speakers

- Liquid biopsies are likely to replace solid tissue biopsies in the near future because they are noninvasive and permit real-time tumor assessment, enabling tumors to be monitored over time.
- Precision medicine is only one part of multi-pronged approach to cancer. It is currently generating a great deal of excitement, but much work remains to be done and the final solution for cancer is likely to come from a combination of different areas.
- Precision medicine trials using master protocols can be successful, but many gene variants associated with cancer are rare, necessitating enrollment of extremely large patient numbers. Even with large numbers of patients, too few patients are enrolled in the rare mutation arms to draw conclusions that change clinical practice.
- Precision medicine trials can be successful in the community setting.
- Prior cancers/treatments are frequently exclusion criteria for precision medicine clinical trials, but they exclude many otherwise qualified patients and may not be scientifically supported.
- Data from completed trials can be mined for information about responders and nonresponders.

Background

The Precision Medicine Clinical Trials in Oncology Symposium was convened at the Grand Hyatt Hotel in Dallas Fort Worth, 8 – 10 November 2017 to help patient advocates in decision making roles learn more about the current state of precision medicine in oncology and to gather input on the design of future precision medicine trials. The specific aims of the Symposium were as follows:

- To employ a framework for gathering feedback from patient advocates about patient issues in precision medicine in oncology.
- To implement the PCORI principles of engagement in development of the symposium and dissemination of the results.
- To facilitate meaningful interaction and idea sharing between advocates and clinical trial leaders that will influence the design of precision medicine trials.
- To Increase the knowledge of advocates in decision making roles about the issues and barriers to precision medicine trials from the patient perspective.

Symposium attendees were 32 advocates from around the United States and 9 speakers representing healthcare practitioners, scientists, advocates, and leaders from the National Cancer Institute.

Symposium Organization

The first day of the Symposium was designed to provide information on the current landscape of precision medicine in oncology, including information gleaned from precision medicine trials. Speakers addressed topics related to clinical trial design, accrual, endpoints, and outcomes.

The second day focused on precision medicine in the community setting, and included perspectives from the NCI Community Oncology Research Program (NCORP; a community-based clinical trials network), physician, and research coordinator. This was followed by a Think Tank with advocates to explore ideas for future trials with the patient perspective. The Think Tank addressed two main issues:

- Identifying barriers to conducting precision medicine clinical trials;
- Solutions and areas of influence to address barriers and advance precision medicine clinical trials.

Organization of these Proceedings

These Proceedings provide an overview of each presentation followed by summaries of advocate questions and answers. (Video links to each presentation are available on the Research Advocacy Network RAN website at www.researchadvocacy.org and can be consulted for further information.) The results of audience polls designed to characterize advocate participants and the constituencies they serve are presented, followed by “aha” moments of understanding and concluding thoughts from advocates. The Proceedings close with Think Tank discussions among advocates that explore ideas for future precision medicine trials.

Welcome and Introduction

Mary Lou Smith, JD and Elda Railey
Co-Founders, Research Advocacy Network

Prior to the Symposium, Research Advocacy Network conducted phone interviews with 4 physicians and an online poll of 27 advocates designed to help determine the agenda.

Results of Physician Interviews

When asked how they would define precision medicine to a patient advocate or patient serving groups, several physicians gave the following succinct definitions:

- The matching of treatments to patient and tumor characteristics.
- Tailoring treatments to the individual patient.

However, the other physicians expressed some reservations with the phrase precision medicine. One preferred the phrase individualized medicine, believing we have not yet attained precision medicine, and was wary of overpromising to patients. Another noted that the term precision may be appropriate in a research context or for surgery or radiation. When describing the approach in a clinical context, the physician preferred the term personalized. The lack of agreement on the definition of precision medicine and the how it should be presented clinically reflects the evolving nature of this concept.

When physicians were asked whether they would include all targeted therapies in the category of precision medicine and/or immunotherapy, they answered as follows:

- Manufactured T-cells are individualized, but checkpoint inhibitors are targeted to the immune system and are not specifically targeted to a molecule. Not precise at this point.
- To be considered precise, need to be able to identify targets of response and reaction.
- Would include targeted therapies such as monoclonal antibodies or small molecules that have a target. Would not include immunotherapies, as they activate the immune system and don't target a specific molecule.

Results of Advocate Polls

When advocates were asked to indicate which topics they most wanted to understand related to precision medicine, the most frequent selections were as follows:

- How is conducting precision medicine in the community different or the same as in academic centers?
- What endpoints are used in precision medicine trials? Are they different from traditional trials?
- What are the challenges of tumor profiling for precision medicine?

When asked what the barriers are to patients participating in a precision medicine trial, the most common reason was being offered the trial or having access to the site where the trial is offered. Costs and the requirement for tumor biopsy were the next most frequent reasons. These answers were used to inform the agenda for the Symposium.

Precision Medicine Information Section

Overview of Precision Medicine: Past, Present and Future

Peter J. O'Dwyer, MD
University of Pennsylvania
ECOG-ACRIN Group Co-Chair, NCI-MATCH Trial Co-PI

Dr. O'Dwyer provided an overview of precision medicine, beginning with definitions in the field and descriptions of various genomic tests. He then discussed molecularly guided trials, including study design issues and specifics of ongoing studies.

The goal of precision medicine is to deliver the right treatment at the right dose to the right patient at the right time. There is concern over the promise versus the reality of this goal, particularly in the clinical trial setting when physicians meet with individual patients trying to decide whether to enter the study. The promise versus reality must be presented realistically, and both parties need to be informed.

When considering molecular testing methods, it is important to ask several questions, such as whether the technology is robust and reliable, whether it can find actionable mutations, and whether patients are likely to benefit. Currently, molecular testing is not standard of care for most tumors, but is instead an option. For most cancers and mutations, the benefits of molecular testing have not been quantified, despite the success of selected individual cases.

Tumors evolve, particularly in the presence of treatment. Biopsies from different regions of the primary tumor can show different mutation profiles, as can biopsies from metastatic tumors. Biopsies from circulating tumor DNA might give a better representation of the heterogeneity of tumor than single biopsy, so these noninvasive liquid biopsies are likely to be incorporated into future precision medicine trials.

Genomics should be considered in the context of tumor biology, which is influenced by many factors. Different types of therapies are being developed for the many possible targets in cancer besides mutations in the genome. These include treatments designed to influence epigenetics, the immune system, and the tumor microenvironment, in addition to stem cell-informed therapy.

Current precision medicine trials have established the feasibility of a molecularly guided approach, although it is too early to judge its benefits. Nevertheless, a molecularly guided approach to cancer treatment is superior to “flying blind” and hoping for the best. Trials targeted to specific patients seem most likely to advance curability of cancer, and this may eventually include multiple treatments that target different aspects of tumor biology.

Audience Questions and Answers

- *What expectations should patients have regarding side effects of precision medicine therapies? Shouldn't a by-product of molecular targeting be minimal side effects? If we had drugs that were targeted only to the aberrant proteins, they might be associated with minimal side effects. Today's medications also bind to the normal protein, which can cause side effects. It is also important to note that molecularly guided therapies may be differentially effective at different times in the*

course of cancer, and patients may be more or less likely to accept side effects depending on where they are in the course of their disease and the probability of cure.

- *If tumors are heterogeneous, is there a danger that biopsies could lead us to a wrong target?* Yes, that is a real concern. That risk varies depending on whether the aberration is present in both the primary tumor and the metastasis. If the mutation is present in both, tumor biopsies would be likely to detect it. If, however, there is an additional mutation in the metastasis that might have a bearing on response to therapy, sampling the primary tumor may miss it, but liquid biopsies may detect it.
- *In several examples of clinical trials, you said that the drug wasn't available, but how did that happen? Why are we accruing patients to that trial if the drug is not available?* There are various reasons for this; for example, the drug may not be available for a given population or may be withdrawn from the market. This is a developing area and is a consideration when incorporating the latest science into trials.
- *You didn't mention sequencing for microsatellite instability-high (MSI-high), which means a lot of mutations in the tumors, and pembrolizumab is approved for any cancer that is MSI high, which seems like standard of care.* Yes. Historically, we've identified that by immunohistochemistry because if the protein is missing, that information is as useful as sequencing. Answer by Stanley Hamilton, MD: The current problem is that no clear biomarker is available to identify patients with high mutation burdens, and that's what is really involved with MSI. That, along with several other key mutations, lead to high rates of mutations throughout the genome. The end result is neo (new) antigens from different protein products that result from all those mutations that lead to response to checkpoint inhibitors. The problem is that there are now 7 or 8 different assays that pick this up; MSI was easiest to do because it's been around a long time and the techniques are well established. The problem now is what to do on a broader scale, particularly because if you look at mutation burden diagram, there is overlap between the number of mutations in the most mutated tumors and the ones at the low end. Only tumors on the upper end of the curve respond even though the mutations are present in lower load tumors. There are not established cut points for mutation burden or mutation load, and this may be different in different tumors. Much laboratory work remains to be done.
- *Because we don't have sequencing standards, results from different sequencing providers may be different. Doctors may not be well trained to deal with this issue.* This question may be addressed in Stan's talk. Different assays may give different results, but it doesn't mean they are wrong. When physicians get the sequencing reports, they have no way of interpreting the strength or weakness of that association.
- *When discussing the definition of precision medicine, we are saying that immunotherapy doesn't fit the definition. Yet some of the best progress seems to be a combination of pathway inhibition plus immunotherapy, so these paths are crossing. Are we going down a road that will inhibit people's understanding by dividing precision medicine from immunotherapy and do we need to consider different terminology?* We are probably in a position now to influence these definitions. First, conceptually, the term targeted therapy indicates that the treatment is targeted toward particular molecular abnormalities. Conceptually, this is a useful way to think because they are different. It makes it clear how you are thinking about a treatment and its effect, which is useful. But the limitation I agree with, that we shouldn't ignore immunotherapies in future iterations of these studies. The combined administration of targeted therapies and immunotherapies is in its early

stages. There is little data to support that this is a widespread phenomenon. Preclinical data suggests that it will be useful, but we don't know enough about it to declare that this is the only way forward. It is definitely a way that has to be explored. In the next iteration of the MATCH trial, these combinations are going to be really important.

- *We talk about sample size and gender in trials, but we don't talk about race. There is a problem getting people of color into clinical trials. When they are in clinical trials, it's important to include those numbers so that we know all patients are being helped by the drug. How do you think we should do that? We are doing this in the MATCH trial. We have about 9% African American, but the population that is under-represented is Hispanic ethnicity. Currently it's about 4-5%, but it should be around 10-11%. So, the representation of minorities in MATCH trial is not quite as high as it should be, but it's close. The bigger question that you raise is, when you get the results, even if you do have significant minorities in the whole population, will you know that an African American patient is as likely as the majority population patient to respond or not get toxicity? That part is a numbers issue. You'll see that each of the subgroups in the MATCH group is a phase 2 study and it only comprises 35 patients in the first stage—some went up to 70. But if you take 10% of 70 patients, that's only 7 patients. Statistically speaking, the likelihood of finding meaningful interpretation in a study like that is not very likely unless you have a huge signal. Usually those questions need to await larger trials. The approach that we are taking in ECOG ACRIN is a scientific one: race is a variable, and we want to know how that and other variables influence clinical response to treatment. We are trying to define how to do that.*
- *There has been recent refinement of diagnosis in clear cell kidney cancer according to gene expressions or cluster analysis. Among these subgroups is one that has the poorest outcomes, and African Americans are overrepresented in this group. Even before precision medicine, this would suggest that African Americans might be tested for this gene expression group that would instantly change treatment and/or monitoring. How does this kind of knowledge fit into precision medicine? The clarification of that fact in kidney cancer came from large trials in which patients underwent genomic testing, and that subgroup of patients with the inflammatory type of tumor is clearly different from rest of the clear cell population. Probably the biggest determinant we can identify is that it is more common in African American patients, but there are many African Americans with kidney cancer who don't fit into that subgroup. Thus, we need to understand race as a variable that is important in defining therapy.*
- *Are the agents being tested in precision medicine trials under INDs or are they FDA approved? In the TAPUR trial, all medications were approved for other indications. In MATCH, several agents are under INDs, but not all. Clarification from audience member: If you are using a drug off indication in a trial, it still requires an IND.*
- *Would data from genomic trials be different in societies such as France that are not as heterogeneous as ours? It appears so. I think that there is insufficient breakdown by race of particular genomic abnormalities across a whole span of tumors. If you take colorectal cancer as an example, there isn't a lot of variability based on race. The key abnormalities driving these tumors are found across all groups of patients with colorectal cancer. But there is certainly room to analyze this further because we know, for example, at some stages of certain tumors, some groups do worse, such as African Americans. There is likely to be a genomic contribution to that. There are likely some genomic differences, but they haven't been found yet. Answer by Stanley Hamilton: The most glaring example we've found of this is MSI. You almost never see this in Hispanics unless they*

have the inherited Lynch syndrome. This is a clear observation that this ethnic group doesn't get MSI high tumors.

- *Other researchers have described differences between blacks and whites in colorectal cancer and between men and women. This seems to contradict what you are saying.* I may not be aware of all of the literature. They may have data that I've not yet seen.
- *In MATCH, 10% of all screened patients had actionable mutations, but in earlier studies it was 40%. Why this difference?* The difference is in how you count an actionable mutation. In the older trial, they counted mutations for which they didn't have a targeted treatment. Actionable is not a scientific term. It depends on how tumors were characterized (breadth of platform) and what abnormalities had treatments available. The availability of drugs was highly variable across studies. In MATCH, the "actionable" mutations excluded those that were known and for which there were currently available drugs. The final actionable rate in MATCH was 19%. The aberration rate is much higher, but we didn't have treatments for all of those mutations.
- *Is there a strong generational genetic component to colorectal cancer and are there studies that have looked at this?* Yes. The risk of colorectal cancer for any of us is 5%. If you have a first degree relative with colorectal cancer, the risk rises to 10%. This impacts the frequency of recommended screening and the age at which screening starts. For families with high rates of colorectal cancer, we recommend very early screening because it is curable if you get it early.

Designing for the Future: Elements in Precision Medicine Trial Design

Barbara A. Conley, MD
Special Volunteer to the National Cancer Institute,
National Institutes of Health,
Department of Health and Human Services

Dr. Conley described the elements of precision medicine trial design, including issues to consider, common designs, and master protocols.

When designing precision medicine trials, it is important to consider a variety of issues such as the intent of the trial and the target population. Numerous practical concerns must also be taken into account, including the evidence for benefit of drug, the rarity of the biomarker in the intended population, the quality of the biomarker and how it will be measured, whether fresh biopsies will be needed, methods for obtaining and transporting biospecimens, and whether or not to use a central laboratory for biomarker tests.

In precision medicine trials, molecular profiling is used to determine actionable mutations. Actionable mutations predict clinical response to specific treatments and are therefore predictive biomarkers. Actionable mutations can include activating mutations in oncogenes that up regulate signaling, as long as there is a medication available against the target mutation. Loss of function mutations in tumor suppressors and pathway inhibitors that can lead to enhanced signaling can also be actionable. Other actionable mutations may include those that predict treatment resistance and those involved in DNA repair.

Master protocols have been developed for precision medicine trials that can be used to examine different types of therapies and tumors. One issue in precision medicine is that many molecular “driver” abnormalities are expected to be relatively rare (for example, present in only 3-8% of cancer patients). Screening for each of these mutations in individual trials would result in high rates of screen failures that could be avoided by grouping the studies together and screening for different mutations at the same time. Ideally, using the master protocols will result in operational efficiency gains that will hopefully bring drugs to patients faster. There are two main types of master protocols. In umbrella trials, patients with a single cancer type are screened for a panel of molecular abnormalities then assigned to different drugs based on the results of screening. In basket trials, patients with many different tumor types are screened for a single target mutation profile. The two types of designs can be combined, as they have been in several recent trials, including MATCH.

Audience Questions and Answers

- *Patients have so many acronyms and unfamiliar names to remember. Some doctors may not even know the names of the cancer drugs. Are there ways to simplify acronyms and drug names? This does sometimes get confusing when the drug doesn't have a formal name or when we are trying to be as generic as possible. We could give patients cards to carry that contain the name of the trial and their medications.*

- *Can trials proceed faster by combining phase 1 and 2, for example?* Some trials have combined phases 1 and 2 with extensions. The FDA has been accepting of various trial designs, particularly in signal finding (early) studies.
- *In phase 1 studies, determining the maximum tolerated dose is not the same as determining the best dose. How do we get closer to the best dose?* Researchers can look at the drug's pharmacodynamics and compare that to a response marker, if one is available.
- *What about the continuous reassessment method and accelerated titration?* The continuous reassessment method follows an algorithm that is more complex than a simple additive calculation, but it may not be superior. Accelerated titration is used more often; in this method, the first patient is given a low dose, and if they didn't experience a toxicity more than grade 2, then the dose is escalated in the second patient, and so on. The first time a predefined toxicity level is reached, you go back to the previous dose.
- *It seems there is value in conducting retrospective analyses for older trials. Can we look at these data to identify characteristics of responders?* Yes, this method is being used, and in fact, was used in prospective/retrospective clinical trials to identify ras mutations.
- *What drives the design for better biomarkers?* There is need for more and better biomarkers, but funding has not been a priority. We do have a study section for this at NCI now. The main thing that will drive biomarker development is when it is accompanied by a drug.

NCI-MATCH Trial: What We Learned and Questions Going Forward

Barbara A. Conley, MD
Special Volunteer to the National Cancer Institute,
National Institutes of Health,
Department of Health and Human Services

Dr. Conley described the NCI-MATCH Trial, including information gleaned and questions for the future.

The NCI-MATCH Trial is the largest precision medicine cancer trial to date based on the number of patients, treatment options, and types of cancer studied. The goals were to provide information about whether targetable molecular abnormalities behave similarly across tumor histologies, find signals that could be pursued, generate information that would improve precision medicine, and possibly provide benefit to some patients. The trial was designed to be nimble so that it could take advantage of new knowledge, as well as accessible, including both community and academic medical centers, and both rare and common tumors.

The design was an umbrella basket combination, in which patients with advanced cancers of different types (basket) were screened at trial entry for different tumor mutations (umbrella). Those who had actionable mutations were then assigned to the study medication that matched their mutation profile. If patients experienced disease progression, they could be assigned to another medication based on the presence of additional actionable mutations.

Enrollment in NCI-MATCH was highly successful, with 6000 patients accrued in approximately 2 years—double the original target enrollment. Most of the patients enrolled were from community centers as opposed to academic centers, and the racial/ethnic composition was similar to that of other trials in the area. Women were slightly overrepresented and some states had much better enrollment than others.

The trial ultimately expanded to 30 treatment arms from the original 10, and 12 of 30 arms (40%) reached the accrual needed for primary outcome analysis. An important discovery in the NCI-MATCH trial was that the rare tumor gene variants under study were rarer than expected in the study population, ranging from 0% to 3.5%. To adequately study these rare variants, tens of thousands of patients would need to be screened. The study is now seeking to enroll patients who have already had next generation sequencing completed on their tumors and show rare variants included in the trial.

When complete, the NCI-MATCH Trial will provide information on response rate, 6 month progression free survival, time to progression, and toxicity. The study has already provided information about the frequency of a wide array of actionable mutations in refractory cancer patients, across different tumor histologies. Correlational analyses are being conducted in an attempt to understand the reasons for response and resistance within study arms. Follow-up of patients in the NCI-MATCH trial is ongoing and results will be published as they become available.

No audience questions available.

Tumor Profiling: The Good, The Bad and the Future

Stanley R. Hamilton MD
University of Texas MD Anderson
Head, Pathology and Laboratory Medicine, MDACC
Deputy Chair for Laboratory Science, ECOG-ACRIN

Dr. Hamilton described tumor profiling, with emphasis on the emerging area of liquid biopsies.

Based on a definition from the Mayo Clinic, tumor profiling is a method of testing that evaluates each person's tumor to determine genomic and other molecular characteristics. The results are used as biomarkers that are targets for, or influences on, therapy in order to improve response to and outcome after directed treatment. Tumor profiling has both good and bad points. Among the good are its wide availability, the availability of companion diagnostic tests for many therapies, and dramatic examples of improved outcomes for selected patients. Among the bad points are the low frequency of actionable alterations in many tumor types, the slow adoption of panel testing, the slow uptake of combination therapies, the variable reliability of tests, the high cost and low reimbursement, and the variable decision support.

Liquid biopsies are the future of tumor profiling. These tests use bodily fluids instead of solid tissue for analysis. The fluid used is often blood, but may also be urine, saliva, tears, cerebral spinal fluid, effusion (i.e., discharge), aqueous humor of eye, mucus, gastrointestinal secretions, or semen. In cancer, the collected liquid is analyzed for intact tumor cells or their parts, such as cell-free DNA, RNAs, and proteins, including those packaged in circulating membrane-bound sacs (exosomes and vesicles).

Liquid biopsies have a number of advantages over tumor biopsies, including less invasive or even noninvasive collection procedures, more extensive sampling of tumor mutations due to perfusion throughout body, the possibility of real time sampling over the course of the tumor due to the short life of analytes in the body, the ability to assess sequential specimens, and lower overall costs. Disadvantages include the emerging nature of the methods, questions about reliability, the low analyte concentrations, high volume of specimen needed, and the sometimes "secret" proprietary algorithms used to determine yes/no decisions.

Even though tumor biopsies are not a gold standard for (they are more of a bronze standard), they do have some advantages. These include the standard acquisition techniques, the ability to view tumor histopathology (which allows tumor classification), the larger quantity of specimen, and the well established analytic methods. Disadvantages include the invasive nature of the procedures, inaccessibility of some tumor sites, variable operator skill, costs, limitation to a fixed point in time, and the limitation to a single part of the tumor (i.e., unable to detect intra- and intertumor heterogeneity).

Tumor profiling has become standard of care in medicine, but challenges in methodological standardization remain. Many different methods are currently available and the clinical questions to be

answered drive the choice of tests. Tumor specific characteristics are not yet certain; some tumors shed more cells and DNA into the blood than others.

Audience Questions and Answers

- *Can you comment on the potential for false positives in liquid assays?* One issue seems to be that the analyte levels can vary week to week. Alterations that seem to be present one week may be gone the next.

Scientific Collaborations for Precision Medicine Trials

J Michelle Brockman, MBA
Senior Medical Science Director
Scientific Collaborations US Medical Affairs
Genentech

Ms. Brockman discussed the participation of Genentech in precision medicine trials.

It takes the presence of cutting edge medicines + diagnostics and genomic sequencing + new technologies to bring new medicines to market for patients. In the 1990s, we had blockbuster drugs that were used to treat broad patient populations, such as those with colon cancer or breast cancer. The next development was targeted medications for specific groups based on the heterogeneous features of the cancer and patient characteristics. In the future, treatments will be more individualized with patient based molecular information, so that a drug is individualized just for you.

Genentech-Roche has supported or sponsored a number of precision medicine trials. These include MATCH, NCI Lung Map, ASCO TAPUR, Exceptional Responder (cases put forward when there is a durable response to therapy), and a specialized program at Genentech called MY Pathway. Genentech likes to partner in these studies and see them extended. Genentech supports MATCH 2.0, for example.

Genentech is taking the information about MATCH and putting it on internal slides so that it can be used to get more support from groups within the company for participation in further trials. One of the most impressive features that helps sell the idea is how rapidly the MATCH trial recruited. Although it may be slower to begin, it's worth it because recruitment is so robust.

The MATCH Trial has been a positive experience for Genentech. Genentech has had medications in four arms of the trial, some of which are continuing and others of which are completed: trastuzumab + pertuzumab target HER2 amplification in Arm J, vismodegib targets SMO/PTCH1 in Arm T, ado-trastuzumab emtansine targets HER2 amplification in Arm Q, and taseleb targeted PIK3CA in Arm I. Genentech is currently in negotiations to open another arm for ipatesertib, which targets AKT mutations.

Audience Questions and Answers

- *How do you think we can make industry and NCI collaborations work even better for future trials?*
Some companies may be under the misconception that, once they include their drugs in these trials, they no longer have any say in the study. They believe that NCI may not be open to dialog or collaboration. That is not the experience of Genentech at all, and it may be a matter of helping companies to understand that.
- *If Genentech has a drug that they want tested, how do they decide whether to test it themselves or put it into a program like MATCH?* Depending on the drug, there is more or less sensitivity on the part of the company to putting it in outside programs. In general, more mature molecules are more accessible for outside programs.

- *In MATCH, did companies keep providing drug to patients who were responding even if they decided that the drug was ultimately not going to be successful in the marketplace?* Genentech does have a policy under which we try to make the drug available for patients who are responding in cases like the one you cite. It's possible there might be a conflict if the drug is discontinued from manufacturing. Answer from Dr. Conley: Within MATCH, we asked for a commitment to a certain number of cycles. The drug at NCI has an expiration date and can't be given beyond that. If the company shuts down manufacturing, it is a problem, but we haven't had many of those issues.
- *What can advocates do to help other companies understand the positive nature of collaboration with NCI?* Genentech and some other companies have strong connections with the NCI. NCI could reach out to companies that have big portfolios and attempt to persuade them.
- *Can we contact NCI and encourage them to reach out to other companies and can we ask you (from Genentech) to talk about your positive experience?* Yes, that would be a good idea to put the various parties in the room to discuss.
- *I'm on the Roche-Genentech Ethics Advisory Board and there is tremendous support for providing medication to patients in clinical trials who are responding to the drug, in cases where the drug will not be going forward into other trials.*
- *How are drugs named?* Initially a drug's name is based on its chemical structure. After that, its target and function drive its name, but the commercial team strives to develop a brand identity. This is proprietary, and is tested in market research.

What We've Learned from Other Precision Medicine Trials

David Gerber, MD
Harold C. Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Study Chair, E4512 (ALCHEMIST-ALK)

Dr. Gerber described his experience with the ALCHEMIST precision medicine trial for lung cancer.

ALCHEMIST is an umbrella platform for early-stage lung cancer clinical trials. This trial plans to enroll 8000 patients for whom adjuvant, postoperative chemotherapy is recommended. The study was designed to make it easy and enticing for patients and physicians to participate; for example, patients could enroll before or after surgery or after adjuvant therapy. Following genomic analyses, patients entered one of three studies: an immunotherapy study, a study targeting EGFR mutants, or a study targeting ALK rearrangement.

The rest of the discussion focuses on the ALK-rearrangement study within ALCHEMIST, which needed to enroll 378 patients. Enrollment in this study has been extremely challenging because of the rarity of ALK positive lung cancers. Thus, although lung cancer is common, with more than 200,000 cases annually in the US, only 3-7% are ALK positive. Additionally, only a portion of these are at the stage needed for enrollment in this study.

Initial participation in the study was lower than expected, although enrollment is now increasing. To date, 2400 patients have been screened at 1249 sites; of these, 2% have entered the ALK trial. Multiple efforts have been undertaken to increase awareness and participation, including regional Champion teams that write letters, make phone calls, attend meetings, etc. Part of the reason for the low enrollment was that we did not anticipate the rarity of ALK+ lung cancer. In our population with early disease, the prevalence is about 3-5% instead of the 5-10% reported for later stage disease. Additionally, many eligible patients were declining to participate. This required protocol amendments to make the study more acceptable to patients. Finally, we reconsidered eligibility criteria, and particularly the exclusion of patients with prior cancers. We undertook studies to examine this and found that prior cancer does not adversely impact outcomes for Stage 1-2 lung cancer, so this exclusion was eliminated from the study. These experiences may be helpful when designing other trials targeting rare cancer mutations.

Audience Questions and Answers

- *Do you have a formal survey that you give to people who are eligible for the study but decline?* We don't have a formal survey but we try to capture that information; responses suggested that the placebo was a barrier to entry, even though it was standard of care, so we dropped it.
- *Why was your estimated accrual rate so much higher than the actual rate?* We are finding that ALK positivity is less common in early disease than in advanced disease (not 5-10%, but 3-5%). Initially, we didn't allow patients with squamous disease to enroll because we didn't have the immunotherapy trial option; now we do have the option and are enrolling these patients, but none

is likely to be ALK+, so that is diluting our numbers. We were also surprised at the number of eligible patients who declined.

- *Did you do any focus groups presenting trial design to ask whether patients would consider enrolling?* Enrollment projection comes from working backwards. The trial was designed with a specified duration that couldn't be increased, and we had to change the endpoint from DFS to OS, so we had to increase accrual. Our initial number was probably overly optimistic.
- *You use prior cancer versus new cancer, but is there a reason why you didn't use primary versus secondary cancer?* Yes. There are many clinical studies on secondary cancers, for example, with people who had Hodgkin's disease and now have lung cancer because of the radiation. That wasn't our question; it wasn't about people who had cancer before. Our question was about people who had lung cancer now.
- *In terms of randomization, did you consider 2:1 or 3:1 randomization or crossover from the observation arm should lung cancer progress?* We do expect crossover to occur because the drug is FDA approved for advanced recurrence (not early stage). When new lung cancer nodules develop, the appropriate treatment isn't an ALK inhibitor, it's surgery to take out the cancer to cure it. It's difficult to do crossover for that reason. The 2:1 and 3:1 randomization wasn't done because of the power concern, which would increase sample size by another third, but that's a question to take back to patient advocates.
- *What is the prognosis for people in Stage 1B-3A without any further intervention? Are there other exclusion criteria that researchers use too much? Should "previous cancer" exclusion also apply to other trials?* Some lung cancers are likely to be cured (Stage 1A; not eligible for this trial); most patients on our trial are Stage 2. The 5-year survival for Stage 2A is 50% and for Stage 2B is 30%. We know that chemotherapy improves outcomes for these patients.
- *What are the potential side effects of drug interventions and if I were a patient how would I compare the risk benefit profile?* Targeted therapy drugs all have side effects and sometimes these can be worse than chemotherapy because, today, we are good at preventing nausea and vomiting and mitigating the low blood counts that are side effects of chemotherapy. Additionally, chemotherapy is done only once every 3 weeks, so the side effects may only occur intermittently. Targeted therapy is taken every day, so lower level side effects can become important. Side effects with targeted therapy tend to have a gradual onset and are rarely life threatening. This allows us time to adjust dose to help reduce the impact of side effects on quality of life.

NCI Community Oncology Research Program (NCORP): Precision Medicine in the Community

Worta McCaskill-Stevens, MD, MS
Chief, Community Oncology and Prevention Trials Research Group
Division of Cancer Prevention
National Cancer Institute

Dr. McCaskill-Stevens discussed the participation of NCORP in precision medicine research.

NCORP is part of the NCI Clinical Trials Network (NCTN) and was formed to engage community oncologists in research, allow them access to cancer trials, and train them in cancer prevention. NCORP is an academic and community partnership that participates in clinical trials for cancer control and prevention, comparative effectiveness, and screening; accrues to NCTN treatment and advanced imaging trials; conducts cancer care delivery research to develop clinical practices that achieve optimal clinical outcomes; and incorporates cancer disparities research into clinical trials and cancer care delivery research.

NCORP is a large network with 34 community sites and 12 minority and underserved sites, including more than 4000 investigators. Since beginning in 2014, NCORP has enrolled about 18,000 patients in clinical trials. Enrollment of minorities is 21% overall, with 15% in community sites and 53% in underserved and minority sites. NCORP sites have enrolled 37% of the patients in the ALCHEMIST precision medicine trial and 44% in the MATCH trial. Patients are enrolled from very different environments, from Manhattan to the fields of Montana.

Precision prevention is an important area for NCORP. We have identified six opportunities/priorities in this area: immunoprevention, HPV vaccine, overdiagnosis, pre Cancer Genome Atlas, surveillance, and tomosynthesis(3D) versus digital (2D) mammography. NCORP has undertaken a large screening trial of 165,000 women with the primary aim of comparing the rates of advanced breast cancer in women undergoing screening with tomosynthesis vs. digital mammography alone. This is the first time tissue has been collected concomitantly from both benign, premalignant and malignant cancers in a screening trial. The goal of this study is to provide information that will help individualize screening recommendations.

Another area of focus for NCORP is precision medicine in symptom science. Symptoms are important to patients, particularly cardiovascular disease, cognitive impairment, cancer pain, fatigue, and peripheral neuropathy. Studies are planned for these areas. In the area of cancer care delivery research, opportunities related to precision medicine include financial toxicities (cost of tests and medications, lost work, travel, etc.) and current practices in the community setting such as biomarker testing and genetic counseling.

Challenges for NCORP include the avoidance of disparities in outcomes from benefits of precision medicine, identifying the best funding model for investigators, identifying strategies to engage oncology stakeholders at the sites, appreciating the complexities of presenting a new generation of trials and

communicating results, and engaging patients and non-oncology partners as “we” work to implement advances and improve the quality of cancer care.

Audience Questions and Answers

- *The definition you cited of precision medicine included a psychological component, which I’ve not seen in other definitions. Could you give examples of where this is used?* The paper in which this definition appeared was looking at the broader perspective as we introduce precision medicine to the community. One example is how patients might feel when they see a precision medicine treatment on television, but when their tissue is sequenced, they don’t have that mutation and therefore don’t receive that medicine. They may feel like they are not getting state-of-the-science care. Another example is that patients might have a mutation for which the significance is unknown. This can have a psychological impact. Without data, patients have ambiguity.
- *People are often excluded from clinical trials because the protocol is not available in their language or the quality of life component in clinical trial has not been validated. What does it take to get groups to make this a priority and is NCORP the vehicle for looking at this issue?* In terms of quality of life, the protocols now must include quality of life tools for which there are translations. Many of the classical tools are translated. Now the translated versions must be referenced in the protocol so that investigators can find them easily.
- *How are you able to recruit patients so efficiently for your trials?* The trials are often designed so that they can be implemented efficiently and are of interest to the communities. However, not all trials recruit at a high level.
- *We need to be careful about specifying eligibility criteria that is not appropriate because it excludes patients who have actionable mutations and want to enter the trial. Patients may be devastated. I agree that eligibility criteria are important to carefully consider. This has actually been under discussion for decades. Many parties come together to generate these criteria and we need to be sure that the trials are sensitive to all stakeholders.*
- *With regard to the coverage of NCORP, what is the overlap between local oncologists and NCORP, and how many patients have access to trials like you are discussing?* We are attempting to determine this. In some areas we might have an NCORP site with a defined catchment area, but this doesn’t take into account competitors or referral patterns. There is significant coverage but it’s dynamic. There are also some areas of the US that are untouched, such as New England and several southern states. If you overlap the cooperative group sites with the NCORP sites, the US is pretty well covered, but there are still some patients who don’t have access.
- *NCORP has a consistent group of recruiters and I wondered if you have considered lessons learned from those places like metro Minnesota and Southeast Clinical Oncology Research because something they are doing could inform other NCORP sites and academic centers?* Our staff tries to share best practices, but the truth is that there are cultural differences across the country. In some places, people are willing to drive great distances, whereas in others places, people don’t want to walk several blocks. Investigator passion, institutional support, and trial features all play a role. We do hold conference calls to discuss best practices and common issues; for example, insurance coverage barriers were a common problem for which we now have an organized approach.

- *I noticed that for the TMIST trial you only showed 4 sites currently open. How do you decide how many sites ultimately need to open and did you undertake testing at those sites to see if they could meet the accrual rates?* This trial requires engaging radiologists in research, many of whom are not rostered within the system. This trial also requires significant training and we are currently developing a video to aid in this. We do have more than 50 people in the cue, but it takes time for the enrollment to be processed.

Precision Medicine in the Community – An Old Physician’s Perspective

James L. Wade III, MD, FACP, FASCO
Associate Professor of Clinical Medicine
Feinberg School of Medicine, Northwestern University
Principal Investigator, Heartland NCORP
President, Cancer Care Specialists of Illinois

Dr. Wade placed precision medicine in the context of many different promising cancer treatments over the past few decades and described the participation of Heartland CORP in precision medicine trials.

Precision medicine is an exciting development in cancer, but it must be placed in a historical context. Over the past few decades, many waves of promising cancer treatments have waxed and waned. Each wave has come with great hope and enthusiasm, but has left us with some disappointment. This is not because people have failed, but because it is hard.

One such wave was interferon, which many experts thought would cure everything from small cell lung cancer to ovarian cancer. Interferon is still used, but its role is limited. Other waves have included multi-agent chemotherapy, non-cross resistant chemotherapy, bone marrow transplant for solid tumors, biotherapeutics such as IL-2, and antibodies such as bevacizumab for multiple cancers. Each wave has brought progress, but has not proven to be the final solution. For this reason, we need to rein in our enthusiasm for precision medicine. Some successful results have been reported, but these are often heavily influenced by patient variation (ethnicity, background, age, pharmacogenomics, immune response, metabolism, etc.).

Heartland NCORP is an Illinois-based alliance that serves 6 million people and treats 16,000 new cancer cases annually. We are currently involved in 6 molecular target driven studies: SWOG Lung-MAP, ECOG/ACRIN MATCH, NCI Exceptional Responders, SWOG 1403 (A Randomized Phase II/III Trial of Afatinib Plus Cetuximab versus Afatinib Alone in Treatment-Naïve Patients with Advanced, EGFR Mutation Positive Non Small Lung Cancer, and Alliance (Combination Chemotherapy With or Without Atezolizumab in Treating Patients With Stage III Colon Cancer and Deficient DNA Mismatch Repair).

My overall experience is that molecular trials hold promise, but for a few. Over the last 3 years, sequencing and identification of molecular subtypes has grown at a staggering rate. At the same time, payers such as Medicare have begun focusing on cost of care. Medicare is now evaluating cost of care (e.g., sequencing, drug expenses, etc.) in their determinations of reimbursement.

Progress in cancer treatment will require many different solutions. One avenue for exploration is to search closed phase 3 trials of patients with metastatic disease to look for unexpected survivors (expanded, validated data set). Often cancerous tissue and germ line DNA were collected as part of the parent trials and they may produce important clues. Another avenue is to search prevention trials for those who subsequently developed cancer. Would we find early circulating DNA clues? The blood is already stored and the analytic technologies are far superior today than they were in the past.

Audience Questions and Answers

- *What happened to the 90% plus patients who didn't get into the MATCH trial? Did you learn anything from their biopsies?* Their tissue has been sequenced and they may have had mutations for which there was not a target. They went on standard of care, and having had advanced disease, most have passed away.
- *How does the American Affordable Care Act impact your work presently and what do you anticipate its effect to be in the future?* Losing it hurts, having it helped. There were a number of exchanges that opened in our area, but have now closed. People who had never had insurance before got screened and their cancers were detected and treated early; that was exciting to see. It's sad now that it's gone.
- *NCI has formed a committee called Core Correlative Science Committee and they field requests for research with biospecimens that have been previously collected, and it's interesting that they aren't getting more applications to study those tissues.* Yes, there's gold out there we haven't mined.
- *You described a patient with squamous cell cancer whose disease progressed with targeted therapy. What do you think went wrong; do you think the dose was off? How do you think about dosing with targeted therapies when you aren't looking for maximum tolerated doses?* There are many parallel signaling pathways and sometimes we accelerate signaling in another pathway when we block one. The drug might have done exactly what it was supposed to do, but we might have turned something else on as an unintended consequence.

Precision Medicine in the Community: A Research Coordinator's Perspective

Leslie Byatt, CphT, CCRC
Clinical Research Manager
New Mexico Cancer Care Alliance

Ms. Byatt described the research coordinator's perspective on precision medicine research in the community.

New Mexico Cancer Care Alliance is a collaborative, nonprofit community clinical research network. It comprises 5 hospitals and health care systems and includes more than 100 community based physicians. New Mexico Cancer Care Alliance provides education for patients and their families, as well as research support for community practices and hospitals. In the latter capacity, the Alliance identifies, approves, opens, and manages studies, including executing confidentiality agreements, obtaining Medicare coverage, and managing external inspections.

We consider both feasibility and logistics. For instance, we assess investigator/site interest in trials, the patient population, potential hurdles to enrollment, competing trials, site resources, the impact of study procedures on routine care, and the specific sponsor requirements. All participating sites and teams must review the protocol early and thoroughly. In this process, we can identify non-standard practices, the need for increased collaboration, and the need for increased resources. We consider whether the timelines coincide with protocol expectations, the consistency of timelines with standard of care, and assess whether there are specific visit timelines that maybe challenging to subjects. When examining procedures, we consider whether they are consistent with standard of care, covered by insurance or paid for by study sponsors, and additional processes required within a procedure.

Potential areas that may slow the trial process include the presence of multiple sub-studies, the need for clinical team training, and trial logistics. We create processes to streamline submission such as initiating clinical team training early in the process. Our goal is to be proactive not reactive.

Academic and community centers show some differences in the conduct of precision medicine trials. In academic centers, most resources are under one roof, collaborative relationships are already in place, processes are not as flexible, and process changes are slower. In community centers, there is a potential for procedures to be outsourced to third party vendor, relationships must be built with vendors early in the process or even before they are needed, and the process is more flexible.

No audience questions available.

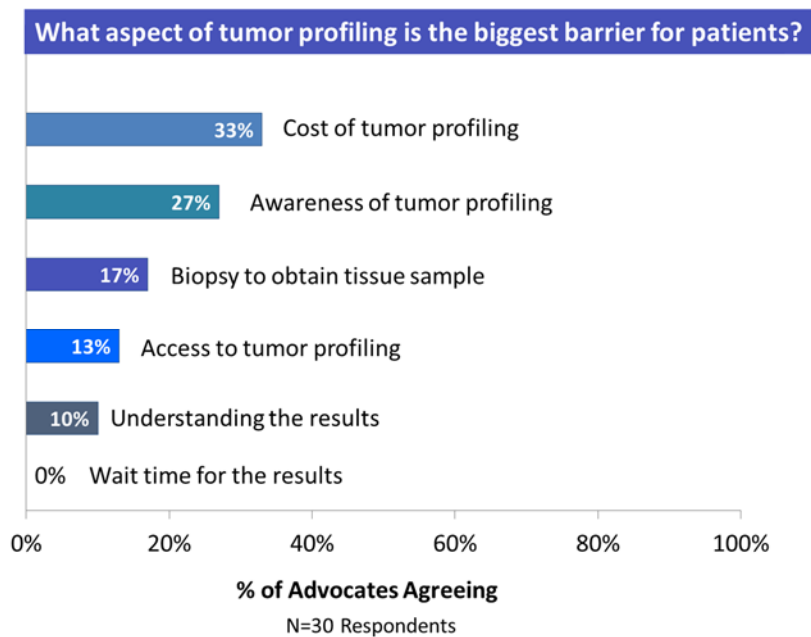
Advocate Think Tank Section

Advocate Audience Demographics

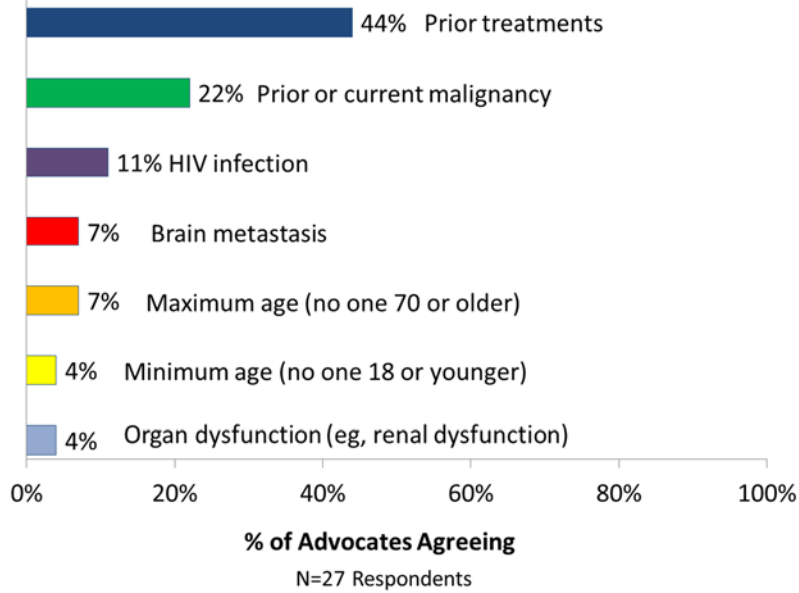
A total of 32 advocates attended the Symposium and responded to a few questions about their background, constituencies, and precision medicine. Most (83%) were cancer survivors and were split as to whether their primary reaction to precision medicine was excitement (41%) or being full of questions (59%). Advocates represented SWOG (31%), ECOG-ACRIN (28%), NCI Steering Committee (17%), the Alliance (14%), and the NRG (10%). Advocates' primary patient constituencies were breast cancer (26%), colorectal cancer (17%), ovarian cancer (13%), and prostate cancer (9%), with the remaining cancers represented by a single advocate.

Advocate Audience Questions on Precision Medicine

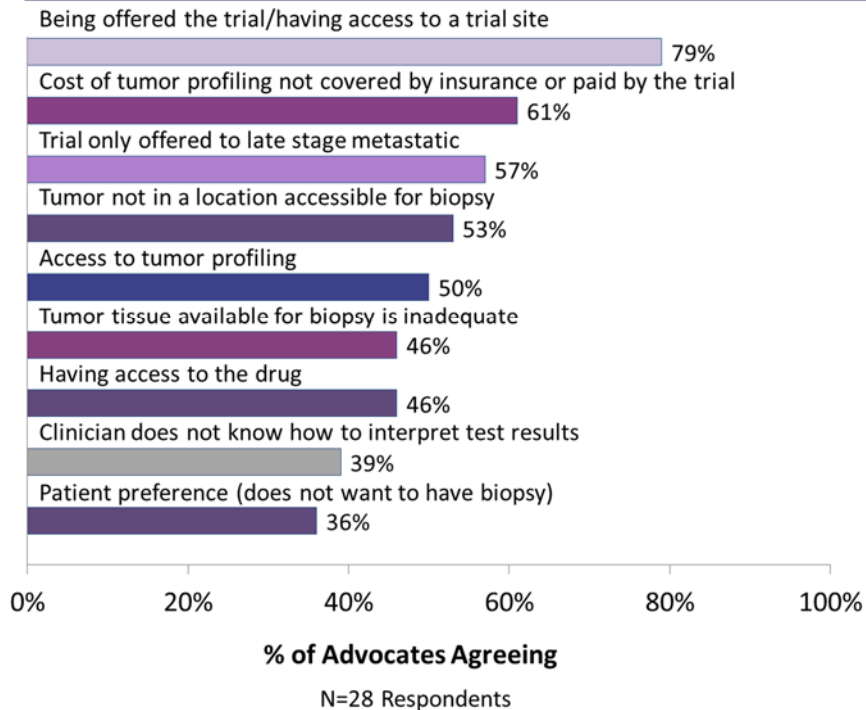
Most advocates (61%) indicated that the patients they serve do not ask about tumor profiling. Advocates believed that most patients get information about tumor profiling from the healthcare team (38%), other medical sites (28%), support groups and chat rooms (24%), and advocate organization websites (10%). Additional results are shown in the following graphs.



Which of these exclusion criteria most limits patient participation in clinical trials?



What are the barriers to patients participating in a precision medicine trial? Select all that apply



“Aha” Moments

Advocates described the “aha” moments and ideas they had during the Symposium.

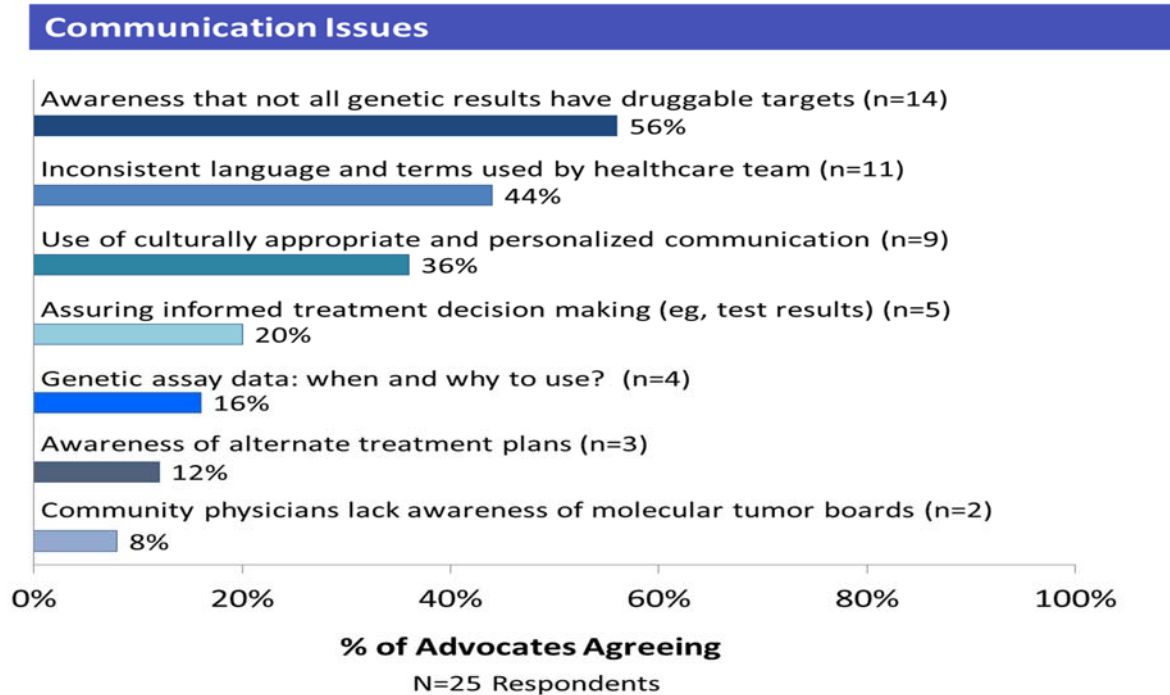
- Liquid biopsies have high value. These biopsies allow you to follow a person’s cancer through treatment, avoiding invasive biopsies like colonoscopy. This helps reassure people that their cancer isn’t popping up anywhere else. Liquid biopsies would also enable tracking of a treatment’s effectiveness over time, to see if the drug is working.
- Are we missing opportunities for collaboration with companies that don’t understand the NCI interface? What do you do to get these other companies involved? Perhaps a collaboration summit is needed to bring parties together.
- There is no biomarker that points to the extent of the mutation burden. Different burdens will affect response.
- “Actionable” doesn’t always mean the same thing in all precision medicine situations; it’s not always used the same way by everyone.
- Can research be patient driven? What do patients want to know? Can we move from research *on* patients to research *with* patients? Suggest change in wording—instead of referring to clinical trial “participants,” can we change to “contributors?” Contributors should be compensated with recognition.
- Patients and researchers should be partners, but not all blame goes to the researchers. We should begin by educating the community on what research is. Researchers have language of their own; patients may feel dumb when they don’t understand it, which is an obstacle. Patients feel they can’t understand. Researchers don’t provide lay abstracts; they assume the community doesn’t want to know. However, community members are excited when they learn about it. We need more discussions about participating in research and getting people excited about what’s going on. The community needs to learn results of clinical studies so that they don’t feel like researchers just want to experiment on them. If patients are viewed as partners, the community can help lobby for research.
- Lobbying efforts are paying off. The National Defense Authorization Act presented to the Senate had language in it to restrict and potentially eliminate the Department of Defense’s Congressionally Directed Medical Research Programs. Due to lobbying efforts from advocates, this language was stripped out of bill.
- The patient community can drive research. Some researchers bring in advocates monthly to consult and may implement a mentoring program in which advocates are placed with a young researcher to teach them how to use language that patients can understand.
- Doctors have just 6 minutes to spend with patients. It’s sad that our society has put physicians under that pressure. They have to treat as many patients as possible and don’t have time to learn what their patients are experiencing.
- Survivors Teaching Students® is a program in which cancer survivors speak in medical school classrooms to explain how they were treated and diagnosed and tell them stories that will help them understand what they will experience in clinical practice.

- Closing the loop, getting information back to patients is important. Patients need thank you letters and studies need provisions to send publications out to patients. Can advocates advise as to the best ways to get results back to patients?
- Patients are taking more active roles in their disease and care. Patients have an obligation to participate. They need to learn to say the name of their medications. They have both rights and obligations.
- American Indian and Alaskan Natives were not mentioned once in this Symposium. Seventy-eight percent don't live on reservations. Why don't researchers reach out to this community? We need to talk about this. The community also includes rural frontier (ranchers, miners, Hutterites, etc.).
- Advocates need to check with their local academic institutions to reach out to underserved populations. Advocates represent diverse communities and need to make sure all voices are heard. We need to develop a map of where to go next, as opposed to just talk. We need a map and metrics to make it happen.
- How are drugs chosen for MATCH? Is the ALK inhibitor used in MATCH the best one or just the one from the company that collaborates with NCI? In the recent past we heard about the \$100 genome promise, but now it seems we are discussing whether patients can afford the test. In the MATCH trial some specimens were inadequate, but the issues were addressed so why is it happening? How long do we have to wait for circulating tumor cell biopsies? Some people in MATCH have multiple targets, how do you decide which one to target?

Think Tank

A Think Tank was convened on the final day of the Symposium to explore ideas from advocates for future precision medicine trials. Advocates were broken out into small groups to address 3 major issues in precision medicine trials: Communications, Logistics, and Clinical Trial Design. Prior to break out, advocates were polled on subtopics within each major topic area to prioritize them; results of this polling are presented at the end of this section.

Communications Group



Among communication issues considered, the awareness that not all genetic results have druggable targets was identified as the highest priority for discussion, followed by the inconsistent language and terms used by the healthcare team. These two topics were selected for more detailed consideration in the Think Tank by the Communications team.

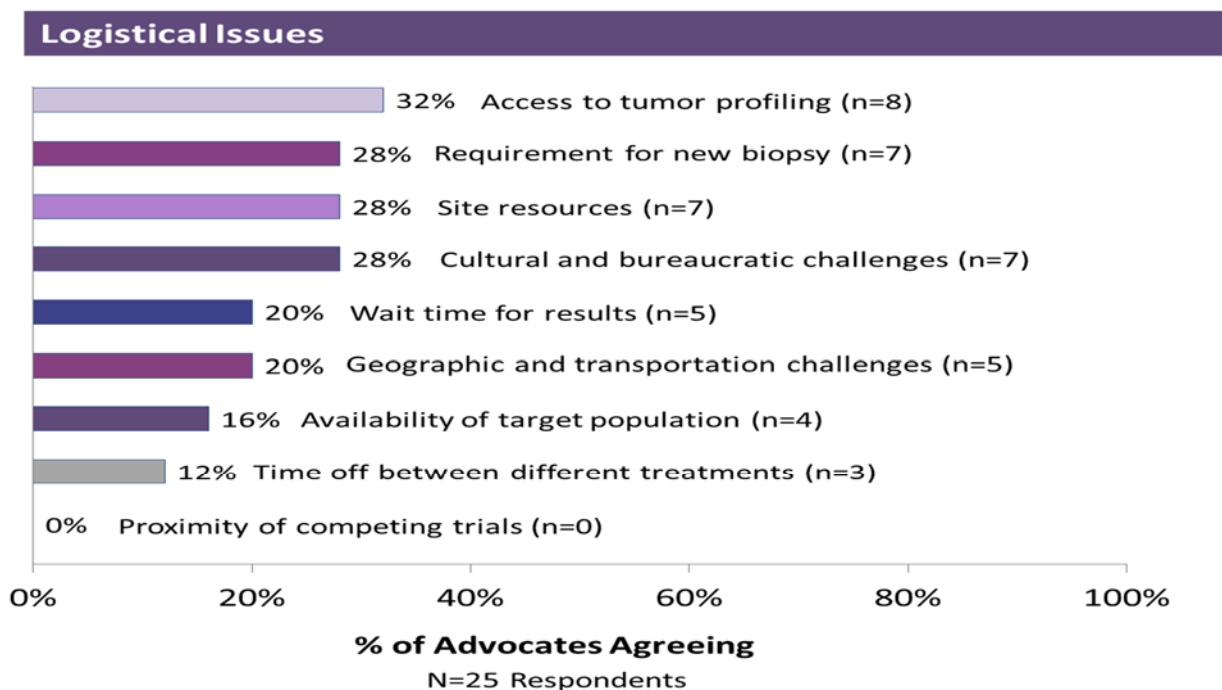
- Awareness that not all results will have actionable mutations

Patients in precision medicine clinical trials are not always aware that their cancers may not have actionable mutations. Although consent forms include this information, it is easy for patients to overlook. Informed consent documents should include a checklist or bullet points to bring this information to patients' attention and the trial should include additional educational material in multimedia formats, such as CDs or DVDs. Different formats would also help patients more fully understand the meaning of actionable mutations and why not everyone has one.

- Inconsistent language and terms used by the healthcare team

Definitions in precision medicine vary, as demonstrated by the speakers in this Symposium—even experts do not agree. Additionally, healthcare team members do not all use the same terms to mean the same thing. Advocates can urge organizations such as the NCI, SWOG, and Alliance to use consistent language, as well as researchers and the medical community. Although it may be difficult to achieve consistent language among all of these groups, the general consensus is that we need to start somewhere. Lungevity conducted a language audit (<https://www.lungevity.org/sites/default/files/file-uploads/testing-terminology-world-lung-2016-poster.pdf>) about what patients hear about biomarker testing that may be a useful place to begin. Moreover, patients need language that is understandable. A glossary would be helpful to patients and their families and could be made available in print and other formats, such as CDs and DVDs. Development of a glossary can be done by different organizations and is not solely the responsibility of the trial organizers.

Logistical Issues



Among logistical issues, access to tumor profiling was the highest priority issue, followed by a 3-way tie between requirement for new biopsy, site resources, and cultural/bureaucratic challenges. A tie-breaking vote identified site resources as the second highest priority topic for consideration.

- Access to tumor profiling

Access to tumor profiling includes several aspects. First, patients may not know that tumor profiling exists and second, physicians may not know how or where such tests can be performed. For this reason, access to tumor profiling may need to be addressed at both the patient and physician levels.

- Site resources

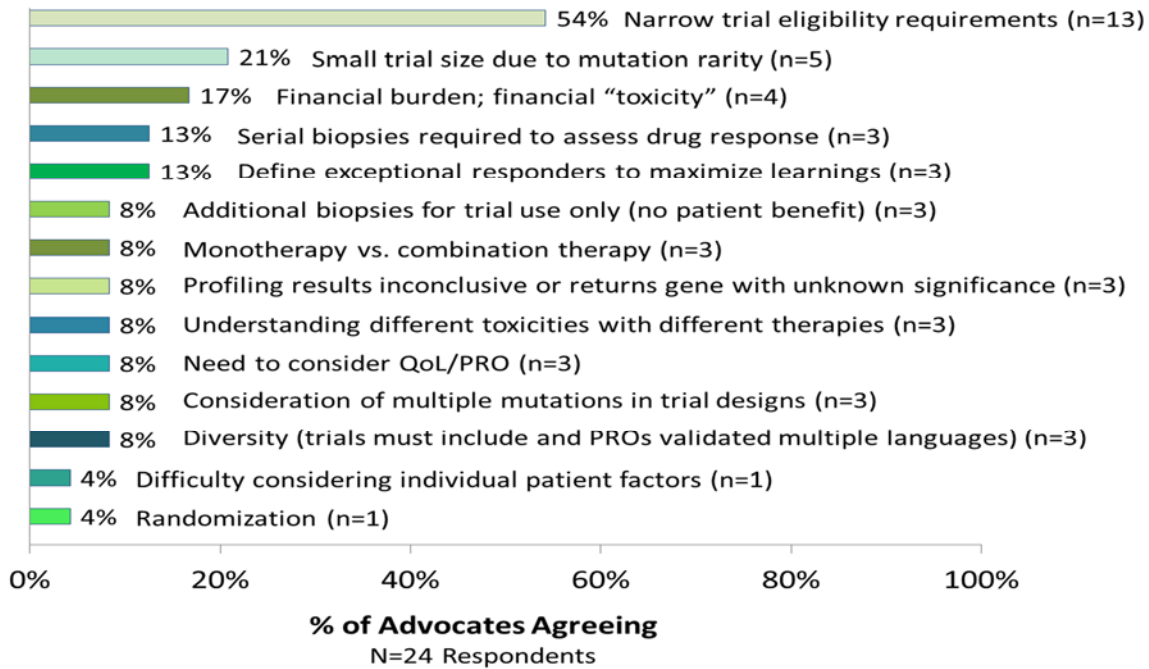
Site resources include physical resources, financial resources, and staff skills, among other things. Centers of excellence should be recognized within communities or cancer networks so that patients know where to go for tumor profiling, as well as to obtain information about the process for themselves and their families. Sites outside the centers of excellence should be identified that can prepare tumor tissue for profiling, and staff should be skilled in handling and storing tumor tissue. Third party vendors should be included to manage tissue handling and storage to promote consistency.

In many cases, patients do not have control over their own tumor tissue once it is removed. This may be problematic if patients later seek to have their tumor tissue profiled to determine whether they might benefit from a certain treatment. However, at the time of tumor removal, patients are not focused on the fate of their excised tumor tissue, but rather on the current treatment and their own recovery. Patients need education regarding the fate of the removed tumor tissue and need contact information for the surgical center that removed it.

Patient consent to use the tissue for research can be an issue. Each state has its own laws regarding how long tumors are held in pathology laboratories. The Common Rule in the Code of Federal Regulations governing human research protections recently changed to allow broad consent for use of tumor tissue. Patients can opt out, but many do not. Patients who opt out of broad consent retain the ability to consent to each individual study that seeks to include their tumor tissue. It's also important to note that cooperating institutions may not cooperate well when it comes to tumor tissue samples. One institution may allow the other institution to take the tissue they need from the biospecimen block, whereas other institutions provide a certain amount of tissue that may or may not be enough for the second center to use.

Financial resources are also a critical consideration, even in clinical trials. Patients may require preapproval from their insurance company to start a clinical trial treatment and may need reimbursement for out of pocket expenses. Private parties may be able to help with this need.

Clinical Trial Design Issues



Among clinical trial design issues, narrow trial eligibility requirements was selected as the highest priority discussion topic, followed by the small size of precision medicine studies and the consequent implications for clinical practice.

- Trial has narrow eligibility requirements and even those with actionable mutations may be denied entry

Many precision medicine (and other) clinical trials have narrow eligibility requirements, such that patients with the mutation under study, who stand to benefit from the treatment, may not qualify for enrollment. Any exclusion criteria must be specifically justified, and exclusion criteria must be removed if not clinically or scientifically supported.

- Small size of precision medicine trials precludes influence on clinical practice

Precision medicine studies can be quite small due to the rarity of individual mutations. This leads to a low number of patients in each mutation group, even though the overall number enrolled in the trial may be quite large. The low number of patients with each mutation may preclude statistically significant results that would support changes in practice recommendations. In these trials, it is important to analyze differences between responders and nonresponders to potentially identify variables that influence outcomes. Additionally, precision medicine studies in which small groups show strong positive results should be able to influence clinical practice recommendations.

Another alternative for achieving statistically significant outcomes despite the small numbers of patients in precision medicine trials is to reconsider endpoints when designing trials. Typical endpoints in cancer

studies are progression free survival and overall survival, but statistical significance in these outcomes can be difficult to achieve with small patient numbers. Endpoints should be continually evaluated and modified as scientifically and clinically indicated. Even relatively small improvements may add up for patients. For example, if one treatment extends progression free survival by 10 months, patients may then opt for another treatment that again adds 10 months, and so forth. Projects evaluating endpoints are currently underway and the results may influence clinical trial design.

Sponsorship

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Abbreviations

ACRIN: American College of Radiology Imaging Network

ALCHEMIST: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

ALK: anaplastic lymphoma kinase

ASCO: American Society for Clinical Oncology

DFS: disease free survival

DNA: deoxyribonucleic acid

ECOG: Eastern Clinical Oncology Group

EGFR: epidermal growth factor receptor

FDA: Food and Drug Administration

HER2: human epidermal growth factor receptor-2

IND: investigational new drug

MATCH: Molecular Analysis for Therapy Choice

MSI: microsatellite instability

NCI: National Cancer Institute

NCORP: NCI Community Oncology Research Program

NCTN: NCI Clinical Trials Network

OS: overall survival

PCORI: Patient Centered Outcomes Research Institute

PIK3CA: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

SMO/PTCH1: smoothed/patched-1

SWOG: Southwestern Oncology Group

TAPUR: Targeted Agent and Profiling Utilization Registry

TMIST: Tomosynthesis Mammographic Imaging Screening Trial