Re-personalizing precision medicine: is there a role for patient-reported outcomes?

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In the opinion of most, precision medicine is the future of cancer therapeutics. By producing response rates well into double digits, and substantially extending progression-free and overall survival, the molecular testing of tumors to select optimal treatment may be a way to justify the high cost of new and emerging therapeutics. The road to this future will likely be long and winding, however, with a string of incremental successes amid inevitable disappointments. Our patients will walk this road with us, agreeing to testing and treatment when those tests come back positive for an eligible mutation. We will ask them to endure likely toxicity for the unknown chance of clinical benefit, often taking treatment for as long as it seems to be working, which can be years of their lives. It would be nice if we could engage them in the consideration of treatment value along the way. In so doing, we would succeed at making precision medicine truly personalized, resurrecting and re-defining the word "personalized" to reflect the patient's perspective.

There are many published examples of including the patient perspective in oncology drug trials. Most of them have used validated patient-reported outcome (PRO) questionnaires, sometimes referred to as quality-of-life questionnaires, in the randomized phase 3 setting.[1-3] This setting allows for well-controlled testing of treatment differences. However, precision medicine trials are different. They tend to be smaller, single-arm tests for efficacy signals among patients who share a common molecular profile. This demands a new paradigm for inclusion of the patient perspective, one that does not rely on large samples and random allocation of patients into treatment groups, at least not in the early stages of precision medicine trials. In this early stage of precision medicine trials, this new paradigm will likely be one more of discovery than of formal hypothesis testing. Traditional hypothesis-driven PRO endpoints are not appropriate in this setting, in part because of insufficient statistical power, but more importantly because these trials are providing an early look at the patient experience of treatment, which is lacking in conventional endpoints. We suggest that this new paradigm is not only in-line with the growing trend toward patient-centeredness, but also scientifically sound, if done with careful thought and a commitment to some standardized approaches. Over time, by adding to the "big data" inherent in precision medicine, this new approach can produce a wealth of information that will serve to include the patient experience into the risk-benefit equation.

Using the ECOG-ACRIN Molecular Analysis for Therapy Choice (MATCH) trials[4] as an illustration, we begin a discussion of how the paradigm for use of PROs in precision medicine can be reconsidered. Scheduled for opening in late summer 2015, MATCH is a "basket" of small trials that will sequentially open and close, establishing whether patients with a range of tumor mutations, amplifications or translocations are likely to derive clinical benefit over a 6-month period and beyond, when treated with agents targeting an identified pathway. The first 4 MATCH studies, briefly depicted in the accompanying table, will test crizotinib, dabrafenib, and trametinib, each in a small number of patients (35 per substudy) who are eligible based on molecular testing results, not primary tumor location. As with most oncology studies, performance status eligibility is 0/1. Therefore, disease symptoms are not expected to be significant at the start of therapy and, where present, they will likely be variable because of the variety of primary sites. Yet, these patients will, by and large, be people whose disease is progressing, so symptoms will likely emerge. Along with the brief time frame (6 months) for the primary study, this makes it challenging, if not impossible, to reliably measure the relevant disease symptoms in the MATCH trials. However, recent presentations by the US Food and Drug Administration (FDA) have suggested a solution to this dilemma that has relevance here: treat physical function as a proximal and clinically relevant common pathway for the impact of disease symptoms on functional status. Fortunately, the PROMIS group has developed and validated a common physical function metric that can be applied in this setting.[5,6] This metric, with a mean of 50 and standard deviation of 10, is referenced to the US general population, providing advantages for interpretation and valuing difference and change scores as well. In addition, other measures of physical function can be (and have been) linked to the PROMIS metric, thereby not necessarily requiring that one use PROMIS questions to derive a score on the common standardized metric. This is an example of what we mean by a standardized approach.

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TABLE Substudies in the Molecular Analysis for Therapy Choice (MATCH) trial

Substudy (n)	Agent	Patient population	Key disease symptoms;[1] Functional status; and Patient preferences	Expected PRO-relevant toxicity[2]	Likely no. of questions (minutes/ assessment)
F (35)	Crizotinib	ALK translocations, *except* lung adeno and anaplastic large-cell lymphoma	Various Physical function Tolerability/preference	Constipation, diarrhea, nausea, fatigue, dyspnea, visual disturbances	20 (4)
G (35)	Crizotinib	ROS1 translocations, *except* non-small-cell lung cancer	Various Physical function Tolerability/preference	Constipation, diarrhea, nausea, fatigue, dyspnea, visual disturbances	20 (4)
H (35)	Dabrafenib + trametinib	BRAF V600E and V600K mutations, *except* melanoma and thyroid cancer	Various Physical function Tolerability/preference	Hand-foot syndrome, pyrexia, chills, fatigue, rash, nausea, vomiting, constipation, back pain, diarrhea, dehydration	30 (6)
R (35)	Trametinib	BRAF fusions, *or* non-V600E, non-V600K BRAF mutations	Various Physical function Tolerability/preference	Nausea, vomiting, fatigue, diarrhea, rash	18 (4)

PRO, patient-reported outcomes
[1]Ideally based on prior burden of disease research. [2]Based on prior report of >40% all grade *or* ≥2% grade 3/4 toxicity.

When planning any trial, particularly precision-medicine trials with prolonged treatment intervals, overall quality of life may be as important to the patient as specific side effects or symptoms. There are many factors that play into one's sense of overall quality of life in this setting, and these can have a tremendous effect on preferences for therapy, as well as the tolerability of therapy (Table, column 5). Domains that we have not typically assessed are important to truly understand the patient experience in the precision medicine context. These include:

- Patient understanding of complex medical information,
- Genetic testing results and how these affect cancer treatment choice,
- Patient-provider communication,
- Patient preference with regard to how involved they are in medical decision making, and
- How much testing patients are willing to undergo (eg, tumor profiling vs germline testing, which requires extra blood draws) if they are not likely to benefit from those findings.

In addition, we should consider the effects of testing results on family members: genetic testing may reveal risks of illness for family members. How should we capture patient preference for communicating results to family members, especially after patients have died? What are the limits of our obligation here? There are also the effects of being "lucky" (ie, having a genetic polymorphism for which there is a treatment agent that may help, versus having a non-actionable mutation with limited treatment options), and how the results of patients who are less fortunate are communicated, particularly with respect to novel treatment options? Do patients who have an actionable mutation have a higher tolerance for treatment toxicity? How do we accurately communicate potential benefit to patients who have an actionable mutation without overstating the potential benefit? This becomes especially important if patients face out-of-pocket expenses for these treatments. Clearly, there are many aspects of patient preference and treatment tolerability that should ideally be tracked. These could be selected on a trial-by-trial basis as knowledge accumulates.

What about toxicity? Symptoms caused by treatment are every bit as important as those caused by disease, when it comes to impact on quality of life (Table). In fact, sometimes the treatment is worse than the disease. This is especially true in the setting of long-term therapies that are continued for disease stabilization or maintenance of remission. In precision medicine trials, new agents carry new and unique combinations of side effects. How do we measure all of them? Clearly it would be onerous if not impossible to capture every toxicity. Here again is an area in which some standardization can provide value. Considering the initial four MATCH trials, we illustrate an example, admittedly arbitrary, of how this standardization can be done. The table lists the side effects one could consider assessing in each of the studies. How did we come up with those? Without solid justification, we propose 2 arbitrary criteria that can

be gleaned from available information on the drug or drug combination in question. We did this because we believe it is vitally important that there be an objective, transparent, standard approach that reflects true equipoise regarding competing risks that can sometimes be overlooked by an exuberant study team that is excited about a new drug. The 2 proposed criteria, offered merely as a starting point for discussion, are PRO-relevant toxicities that have been observed at any grade, in at least 40% of previously treated patients, or that have been observed at grade 3 or 4 levels in at least 2% of patients. Using those criteria, we identified 5-11 PRO-relevant toxicities for each of the MATCH substudies. Each of those identified toxicities could then be assessed in the relevant trial, using resources such as the National Cancer Institute-sponsored PRO-CTCAE questionnaire[7] for item content.

To personalize precision medicine, we are compelled to find ways to engage patients in the evaluation of new therapies. In addition to treatment toxicities, this includes patient understanding of genetic results and how this affects their current and future treatment options, patient preferences for medical decision making and treatment value, and patient education and support with regard to discussing results with family members. By capturing this information directly from patients, we can begin to truly personalize precision medicine in oncology.

A final note is that these assessments need not be lengthy. A small number of questions, asked fairly frequently, can be more informative than a large number of questions seldom asked. The Table shows how many questions (with number of minutes in parentheses) are likely to be necessary to assess the selected endpoints. The rough estimate of the number of questions was based on 4 each for physical function and tolerability/preferences, and 2 per identified toxicity, all carefully selected. More important than the number of questions is the nature of those questions, and the thought behind selecting them. In early precision medicine trial, there is good reason to challenge the conventional wisdom that only validated scales should be used. Although well-validated scales have tremendous advantages in comparative clinical trials, they are not always the best choice for every purpose. Using validated scales in early precision medicine trials without careful consideration, can stifle creativity and progress. Sometimes (but not always), use of a validated scale in a clinical trial simply because it is valid, is like looking for one's keys under the lamp post because that is where the light is shining. Precision medicine trials may be a good case in point. First, let's ask where those keys are likely to be. Then, using a standardized approach, we can begin to look there with the right questions.

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