

Ethical Considerations of Neuro-Oncology Trial Design in the Era of Precision Medicine

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Introduction

The successes and potential of precision medicine have also introduced new challenges not only related to clinical care, but also to ethics of clinical research. While there remains little doubt of the potential improvements in efficacy with precision medicine, characterizing and understanding these challenges can uphold the standards of patient autonomy, respect, and protection.

Ethical Challenges

Informed Consent

The rapidly changing landscape of genomic medicine requires physicians to understand the theory of precision medicine and be familiar with various therapies in order to inform patients of their options. Physicians differ in their levels of knowledge and experience with precision medicine, which may preclude the ability to provide adequate informed consent. Even for physicians with knowledge on the topic, the limited health literacy of patients combined with complex medical jargon can opacify treatment options. The complexity of genomics in neuro-oncology and targeted therapy mechanisms may fortify the communication barriers that already exist between physicians and patients. Informed consent requests must incorporate options for communicating incidental findings.

Societal Value

Each individual targeted therapy requires significant financial investment for research and development and is

applicable to a narrow spectrum of patients, limiting its societal value. However, oncology should not be an "either-or" enterprise. As public health initiatives combat risk factors like cigarette smoking and obesity, the average lifespan continues to increase and age is an unmodifiable risk factor for many cancers.

Generalizability

In practical terms, a clinician determining whether to prescribe a new targeted therapy to a patient based on the results of a trial with two enrollees may be unable to determine whether their patient will respond similarly to those enrollees. If those enrollees also responded differently to the therapy despite having the same mutational profile, the clinician cannot accurately predict which enrollee the patient would respond more similarly to. Brain pathologies also face the unique challenge that therapeutics must cross the blood brain barrier.

Oversight

The specificity of targeted therapies could increase the difficulty of accumulating sufficient preclinical evidence to justify any trial. Testing therapies that have not been proven to achieve therapeutic levels in the brain would bring further ethical challenges related to patient safety.

Vulnerable Patient Selection

Brain pathologies and their therapies may subtly alter a patient's decision-making capacity. The poor prognoses of many

brain cancers may incentivize patients to explore experimental treatments. These problems are exacerbated for late-stage patients and those with refractory disease, such that these vulnerable patients may become the most eager group to join trials.

Justice

The selection criteria for early phase targeted therapy trials will include specific genetic data that necessitate access to genetic sequencing technologies and the expertise to interpret genetic data. Patients of low socioeconomic status may not have equal access to these resources that are often located in advanced tertiary care institutions. Consequently, both the enrollees and beneficiaries of these trials are more likely to be patients of high socioeconomic status, thereby excluding patients of low socioeconomic status.

Potential Solutions

Innovative informed consent structures such as tiered and multi-disciplinary approaches to educate patients will aid in this process. Informed consent processes must also include options for the patient to determine how to handle such scenarios. Many centers currently include these scenarios in informed consent processes, though no consensus has been achieved on the optimal way to accurately convey this information. While long-term societal value of an innovation is difficult to predict, the clinical and scientific benefits from targeted therapies should be recorded and analyzed to determine their true cost-effectiveness by unbiased third-party institutions with the expertise

References

McGowan ML, Settersten RA, Jr., Juengst ET, Fishman JR. Integrating genomics into clinical oncology: ethical and social challenges from proponents of personalized medicine. *Urol Oncol.* 2014;32(2):187-192.
 Budin-Ljosne I, Harris JR. Patient and interest organizations' views on personalized medicine: a qualitative study. *BMC Med Ethics.* 2016;17(1):28.
 Bredenoord AL, Onland-Moret NC, Van Delden JJ. Feedback of individual genetic results to research participants: in favor of a qualified disclosure policy. *Hum Mutat.* 2011;32(8):861-867.

to conduct economic analyses in biomedical fields. The composition of oversight committees will need to reflect the diversity of the geneticists, oncologists, and biologists who contribute to the development of targeted therapies.

Likewise, trial participants themselves should be representative of society and should not be limited to only those who can afford access.

Novel trial design paradigms may mitigate many of the ethical challenges. Large-scale multi-institutional studies increase sample size, thereby increasing the societal value and generalizability of a study. Other emerging clinical trial designs that might mitigate some of the ethical challenges include blinded single participant "on-off" studies, increased enrollment from community centers, seamless phase II/III studies, and Bayesian adaptive randomization models amongst other solutions that also bring their own new ethical challenges.