Virtual Trials and Conditional Approval:
Creating Better Options for Patients With Brain Cancer

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The first advances in oncology occurred at a time when there were no regulations. Doctors had ideas, and put them to work immediately. They adjusted and combined treatments as needed until they were optimized and became standard treatments. Many types of cancer were cured by this work. However, in today's regulatory climate, this is no longer possible.

For most patients with glioblastoma, the prognosis remains grim: average survival with currently approved treatments is less than 2 years. These patients can't afford to wait a decade or more for new drugs to go through the regulatory process.

The good news is that the oncology drug development pipeline for GBM is full of promising targeted- and immuno-therapies, many of which have already been approved for treatment of more common cancers. These drugs are, in principle, available today off-label, in trials, and through compassionate use programs. However, no one knows the optimal way to use these 'available' therapies, because they are seldom tested head to head or in combinations. When used off label, nobody is tracking the results, dooming patients to repeatedly using bad combinations and not quickly identifying the best combinations.

Testing multi-drug regimens in clinical trials is problematic because of the explosive combinatorics. There are at least 4 distinct molecular subtypes of GBM, and several dozen plausible therapies for treating each of them. Which interventions are optimal for treating a given individual over the course of their disease – and in what sequence, schedule and dosing? Current clinical trial designs, including contemporary "adaptive" Bayesian designs, cannot efficiently search this huge combinatorial space, especially given that fewer than 5% of the 20,000 GBM patients diagnosed each year participate in trials.

In the absence of definitive clinical studies, the fastest way to improve outcomes is by aggregating the insights, experiences and intuitions of our best clinicians, and continuously validating and refining them based on real-world outcomes data. Every day, patients who have exhausted the standard of care are treated with off-label drugs and rational cocktails. Unfortunately, these individualized ('N-of-1') experiments are uncoordinated, and their results seldom reported, so little is learned. If we can capture these results and rapidly share them with community oncologists on the front lines, we're confident many lives can be saved – or at least meaningfully extended.

Improving the efficiency of clinical studies won't count for much without timely and affordable access to drugs. Developing a new cancer drug takes about a decade and a billion dollars, much of which is expended in clinical trials. While in trials, an investigational drug is only available to a few percent of patients. Once approved, the average price of a new cancer drug is well over $100,000 per year. For investigational drugs, combination testing cannot even begin until the drug is approved. What if a new treatment was not effective as a monotherapy, but could be an essential component of a multi-drug cocktail, say to block a resistance pathway? Catch 22. Many good ideas will never get to patients.

We propose two bold and synergistic initiatives that address these issues: Virtual trials and Conditional Approval. **Virtual trials** capture treatment and outcome data at the point of care, and use that information to inform future treatment decisions, thereby transforming the everyday practice of oncology into a global adaptive search for better treatments and cures. **Conditional Approval** facilitates drug access by creating a new regulatory pathway whereby any physician can treat an advanced cancer patient with promising investigational drugs that have demonstrated safety and a biological effect in a small group of patients. Patients receiving such therapies would be required to participate in a Virtual Trial, where their treatments, outcomes and side-effects could be captured and used to rapidly improve the outcomes of future patients.

Virtual Trials

Virtual trials will connect patients with expert physicians, and capture their treatment recommendations and rationales in a registry, along with the patient's clinical results. This information will be analyzed and rapidly disseminated to other patients and professionals at the point of care through a *Virtual Trial App (VT App)*. Register a new case and the VT App will display all treatments, trials, and combinations that have been tried by similar patients, sorted by most effective, most cost effective, best risk / benefit ratio, cost, or least side effects. The decision to try a specific therapy, alone or in combination, is always up to the treating physician, who can consult with peers through a network linked to the registry. Patients and physicians will be queried periodically to learn what they did and how well it worked.

The VT App can also suggest what else to try, based on recommendations elicited from experts and molecular tumor boards while they're consulting on similar cases. The App can facilitate the rapid testing and refinement of these hypotheses by coordinating treatment decisions across institutions to rapidly replicate successful strategies and discard failures. In equipoise situations, treatment recommendations can be randomized to maximize learning. Community doctors and experts will be able to discuss cases and treatment options in an online forum.

We will develop and deploy the Virtual Trial Registry and App, and "prime the pump" with treatment insights from neuro-oncology experts and tumor boards. We will engage patients via social media and through partnerships with leading advocacy groups, and recruit physicians through collaborations with large health networks such as California's Sutter Health and the US Veterans Association. Ultimately, we envision all practicing oncologists entering their cases and insights, performing searches on behalf of their patients, and reporting outcomes. By engaging patients and physicians at the point of care, Virtual Trials have the potential to optimize and extend the use of available therapies far more efficiently than traditional clinical trials. Even better, patients are matched to the treatments most likely to benefit them, rather than to trials that happen to be locally available. The resulting trove of public knowledge and data, together with the system's open architecture, will catalyze the medical and AI communities to create many new system extensions, applications and services. We will launch a peer reviewed open source "app store" into which anyone can submit software for, say, decision support or trial finding

Conditional Approval

Conditional approval is a novel regulatory pathway we are discussing with the FDA to accelerate access to promising drugs for GBM and other dire cancers. Conditional Approval would be granted to treatments that **h**ave been proven safe in a clinical trial(s) with at least 50 patients, and have demonstrated biologic activity: an improvement in a biomarker, brain scan, progression free survival or overall survival.

Once approved, the treatment could be offered as if it had a standard approval, and could not be denied by insurance as being "experimental". However, all patients who use a conditional treatment would be required to participate in the Virtual Trial registry for the duration of the conditional approval period, and to sign a consent form acknowledging and agreeing to the risks inherent in undergoing a treatment whose safety and efficacy have not been fully tested.

The FDA would conduct periodic reviews of this registry data, with three possible determinations: 1) If the safety is questionable or if the results look worse than the standard treatments, conditional approval would be withdrawn, and the manufacturer could continue on the standard paths of approval. However, the FDA could not use these results against the standard approval tracks, as the patient population was not controlled and patients were combining other treatments with it; 2) If the results look at least 20% better than the standard treatments, in the first 50 patients over a predetermined period of time, full approval is granted; or 3) If the results are similar to standard treatments, the conditional approval is maintained until the review shows either the treatment is good enough for full approval or bad enough to withdraw approval.

As above, the decision to try a conditionally approved drug, alone or in combination, would normally be up to treating physicians, in consultation with their patients, peers and decision support tools like the VT App. However, the VT App could also support low cost point-of-care 'registry trials,' whereby willing patients are dynamically assigned to treatment arms based on expert recommendations and clinical outcomes for similar patients. We plan to commission an informed consent video that patients will be required to view before participating. To ensure their consent is truly informed, patients will have access to the VT App, as well as expert consultations from the Musella Foundation and Cancer Commons.

It is painfully obvious that the way to cure our currently incurable cancers is to use a combinational approach. We may well have the necessary tools available today—but we are not allowed to use them. When faced with certain death, we believe it is acceptable to not have 100% proven safety and efficacy. We will be approaching the FDA with a request to pilot conditional approval in brain cancer – because life and death decisions should not be made based on regulations – they should be based on what is best for the patient, as determined by the patient and his/her doctors.

Benefits:

Virtual Trials and Conditional Approval offer patients a chance to live, provided they're willing to take reasonable risks. Benefits include faster and more affordable access to a wider range of treatments, including combination treatments; the ability to choose more intelligently among these expanded

options, based on clinical data and expert recommendations; and most importantly, the right to use what they and their physician believe is the best experimental therapy for them, regardless of whether there's a locally available trial, with the right inclusion and exclusion criteria, and without the risk of being randomized to a control arm.

For pharma and biotech companies the benefits are primarily economic – the opportunity to slash the time and cost of drug development 90% or more, by replacing phase 2 and phase 3 trials with a registry-powered Virtual Trial that actually improves our ability to learn what works best for a given patient. Ideally, the Virtual Trial will cover all patients and physicians, and all treatments, all of the time (i.e., patients are automatically included unless they opt out), which minimizes accrual issues and maximizes learning. These efficiencies should allow the industry to sell drugs at a more realistic price (expanding the market); to discover promising new indications, off label and in cocktails; and to explore financially riskier approaches that have the chance to cure diseases instead of safe options that make small improvements – ideas that are impossible to raise funding for under the current system.

Finally, our proposal will help the FDA fulfill its mission to provide the public with safe and effective medicines. Benefits include testing therapies in more representative populations; continuous post marketing surveillance, beginning with phase 1 studies; and accelerating the time to clinic for promising new drugs. Under other proposed and enacted accelerated access pathways (e.g., Right to Try, Fast Track, Breakthrough Therapy, Expanded Access, 21st Century Cures) drug companies are not obliged to provide drugs, and seldom do for fear of FDA holding results from an uncontrolled study against them. Moreover, there's no obligation to track every patient's experiences. Our proposal addresses both of these limitations.

Conclusion

How many cancer patients are dying prematurely because no one knows the optimal way to treat them with currently available drugs? We propose to answer this question first for Glioblastoma Multiforme, among the deadliest and most difficult to treat of all cancers. By continuously learning from the experiences of every participating patient and physician, and immediately applying that knowledge to inform treatment decisions, Virtual Trials can simultaneously optimize individual outcomes and therapeutic regimens far more efficiently than traditional trials. Given the wide variation in treatments and outcomes across institutions, and the challenging combinatorics of testing multi-drug regimens, we are hopeful our approach can provide many patients with years of high quality life. While adoption of Conditional Approval would improve the odds, there is no shortage of promising things to try even under current regulations; using approved drugs off-label and in cocktails, for example, as well as investigational drugs available through trials and compassionate use. If the GBM pilot succeeds, we will quickly replicate it across all major cancers, confident of saving many thousands of lives a day.