VIRTUOSO: Virtual clinical trials concept to help identify resistant tumors

The use of anti-cancer drugs (chemotherapy) is one of the standard-of-care therapeutic treatments routinely applied in clinics. However, a significant portion of patients who show a good initial response to the chemotherapeutic treatment become unresponsive to the drug after multiple cycles; that is, they develop resistance to the drug. Being able to predict early, such as at the time of the pre-treatment tumor biopsy, how the patient will respond to standard chemotherapy would provide an opportunity for more personalized patient care. That is, patients with unfavorable predictions could be provided with individualized treatment protocol, rather than a standard setting to improve therapeutic success.

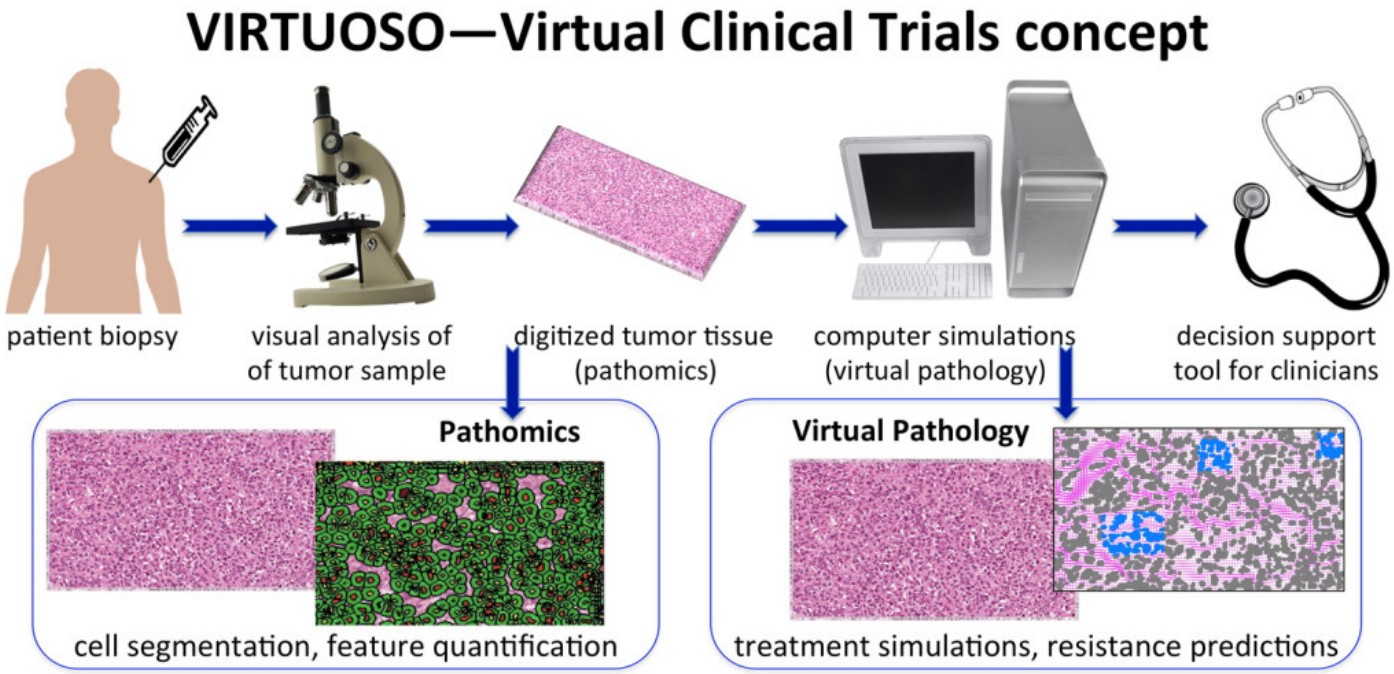

Fig. 1. VIRTUOSO - virtual clinical trials concept

In our recent publication we proposed that computational simulations properly calibrated to individual patients' data extracted from pre-treatment biopsy can be used to predict how a given tumor will respond to chemotherapeutic treatments. We designed a specific protocol for using the Virtual Clinical Trials concept for predicting chemoresistance of osteosarcoma tumors (VIRTUOSO).

Osteosarcoma is the most common primary bone tumor in pediatric and young adult patients. Initial

diagnosis is usually made by a biopsy, in which a small tumor tissue is removed and inspected under the microscope. Successful treatment requires a combination of surgical resection and systemic chemotherapy, both neoadjuvant (prior to surgery) and adjuvant (after surgery). The degree of necrosis following neoadjuvant chemotherapy is a measure of tumor sensitivity to the drugs. In our paper, we hypothesized that the viable cells remaining after the chemotherapeutic treatment, i.e., cells that have not responded to the chemotherapy, are chemoresistant. Moreover, we postulated that the pathological characteristics of these chemoresistant tumor cells within the osteosarcoma pre-treatment biopsy can predict tumor response to the standard-of-care chemotherapeutic treatment.

Our procedure for testing this hypothesis includes generating a high-resolution image of the patient's tumor tissue, and use of computational methods to analyze all individual tumor cells, and then simulate on the computer how the tumor will respond to the standard-of-care treatment. For the first task, we will compare patient histopathology samples taken before and after the chemotherapeutic treatment, and identify both morphological and immunochemical cellular features that are characteristic of chemoresistant cells, i.e., cells that survived treatment. For the second task, we will use specially designed computational models capable of predicting dynamic changes in tumor pathology under the simulated chemotherapeutic treatment. Taken together, our Virtual Clinical Trials procedure—VIRTUOSO—will provide a likelihood of whether a given tumor is or is not chemoresistant.

Our VIRTUOSO predictor will be first trained on a set of data from patients of a known progression-free survival status that we will retrospectively collect from the Moffitt Total Cancer Care database. Patient histopathology samples from before and after treatment will be compared using advanced image analyses (pathomics), feature classification methods (biostatistics and morphometry), and computational simulations of tumor progressions (virtual pathology). This will lead to the identification of patterns of cellular features that are characteristic of chemoresistant osteosarcoma cells (the cells that survived the therapy). Subsequently, our validated predictor will be used for prospective studies. In this case, the pre-treatment biopsy samples will be analyzed and compared with previously identified features of chemoresistant cells, as well as with the previously created library of the simulated results that determine tumor response to treatment. This will allow for calculating the likelihood of the given tumor being chemoresistant.

This predictive tool can serve as a novel value-added decision support tool for oncologists.

Publication

Diagnostic assessment of osteosarcoma chemoresistance based on Virtual Clinical Trials.
Rejniak KA, Lloyd MC, Reed DR, Bui MM.
Med Hypotheses. 2015 Sep