Bedrock: An Intuitive and Interactive Immuno-Oncology App

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Abstract

Introduction

Most patients with late-stage metastatic cancer present with multiple metastatic lesions in multiple organs. Understanding the dynamics of those tumors over time is critical to both doctor and patient as they make treatment decisions and try to understand the course of each patient's disease. During systemic therapy, it is common for some tumors to respond while others continue to grow (oligoprogression) [(1)]. Further, new tumors can appear while responding tumors can rebound. It is difficult for patients, doctors, and researchers to visualize this complexity from radiology reports (including structured radiologic reports) [(2)]. Here we report on a software that we developed that intuitively and interactively visualizes the evolution of every lesion over the course of treatment. We propose that this software will be useful for patients, oncologists, researchers, Quantitative Systems Pharmacology (QSP) modelers, and students. The tool can be particularly useful during clinical consultations as well as multidisciplinary team (tumor board) discussions. Overall, we propose that a next generation data integration/visualization tool will allow doctors, patients and research teams to generate a rapid and deep understanding of individual patients' and aggregate data.

Many patients with cancer have difficulty understanding what is happening to them. This makes it hard for them to meaningfully participate in their own medical decisions. To address this longstanding issue, initiatives such as the patient bill of rights have been developed [(4,5)]. This provides patients with access to their own medical records. However, these records are generally written in dense, unstructured, highly technical jargon that cannot be understood by most cancer patients [(3)]. Ultimately the impact of access to records is therefore impeded by their incomprehensible nature. Several studies have shown that this lack of understanding limits the patient's ability to participate meaningfully in their treatment decision[(3,6)]. As a result, several attempts have been made to develop patient-friendly radiology reports[(7,8,9)]. While these approaches have had some impact, we argue that a next generation, patient-friendly radiology report can further enhance doctor-patient communication both in the office and via telemedicine.

In addition to sharing radiology reports with patients, oncologists and radiologists often share data with tumor board members and other health professionals as part of the therapeutic decision-making process. Sharing electronic health records such as radiology images and reports can be difficult. Several companies have developed software to facilitate rapid analysis and easy sharing of electronic medical records[(10,11,12,13)]. However, none of these software systems visualize time dependent evolution of individual tumors in each patient. We suggest that incorporating this level of detail can improve clinical decision making.

In the context of clinical trial treatments, medical monitors and clinical scientists generally utilize excel-like spreadsheets to track clinical trials. Massive spreadsheets are generated with individual patient data, with different data appearing in different spreadsheets (for example, a spreadsheet to convey pharmacokinetic (PK) data, tumor size data and adverse events (AE) To aggregate and interpret these data, tables are generated to summarize the number of patients enrolled, receiving drug, showing a response, or showing an adverse event. Also, radiology data is generally analyzed at the patient level (RECISTv1.1 response or sum of target lesions). There is clearly an opportunity to integrate this data into an intuitive and interactive data visualization software. This would allow scientists to quickly visualize trial data for any individual patient, any cohort (by plotting population level data) or comparison

between arms (by plotting trial level summaries). Further, the inclusion of individual tumor level data can help monitors decide if treatment beyond progression is justified, allow scientists to see if discern the cause of RECISTv1.1 progression (growth of Target, Non-Target, or appearance of New Metastatic Lesions), and allow biomarker PK scientists to see if response and/or AE are correlated with certain biomarkers or exposure. Overall, we propose that a next generation data visualization tool will allow teams to generate a rapid and deep understanding of their data.

Visualization software can also be applied to simulated data. Pharmaceutical R&D is increasingly reliant on simulated outcomes to facilitate decision making[14,15,16]. While these simulations have generated value, they suffer from two primary challenges: useability and transparency. Systems pharmacology leverages knowledge of human physiology to project clinical outcomes for novel drugs. The stakeholders that are invested in the simulation results are generally MDs and biologists that generally lack formal training in mathematics and coding. This can act as a barrier to understanding integration of systems pharmacology models into formal decision-making processes. Several systems pharmacology software systems have been developed to address these issues; however, these systems remain inaccessible to most pharmaceutical decision makers[17]. We propose that an intuitive and interactive software program can allow MDs and biologists to run QSP simulations and better understand the results.

Over the years, oncology has been taught to students via several mediums including textbooks, slides, and videos. There is increasing evidence to suggest that gamification of education results in higher retention and more intense interaction with the course material[18,19,20,21]. The creation of an interactive game that allows students to build then treat virtual cancer patients, has the potential to engage students on a higher level than other methods. Virtual patients can present with symptoms. and the medical students can then order virtual tests, make a virtual diagnosis, then prescribe virtual therapy. The virtual patient will then respond accordingly and provide the student with the expected outcome. The virtual attending can then show the student what should have been done and show how the outcomes would have differed. Training on virtual patients can be less intimidating, less risky, and more informative than training on real patients.

Overall, we have developed a software named Bedrock that visualizes individual tumor dynamics of individual patients or cohorts of patients. This software can also predict clinical outcomes for novel therapies and provide training simulations. We propose that this software will help patients, oncologists, researchers, and students.

Methods

Software

The Unity Game Engine was used as the foundation on which to create this software application. It is an iPhone App that can be downloaded from the Apple App store. The software can also be downloaded onto a computer (Mac or PC). The software was broken into 5 distinct sections: 1) patients, 2) doctors, 3) clinical investigators, 4) QSP Modelers, 5) Students.

Bedrock MD,

- Code was written to generate a human silhouette
- Code was written to allow patient data for tumor size and location to be imported
- Code was written to transform the tumor data into a visualization of circles on the patient
- The size is approximately accurate. Color was chosen based on xxx
- Code was written to visualize change in tumor size over time on the silhouette
- Graphs were created by …
- Code was written to allow for update of each patient as new data is available

Results

A Patient Friendly Radiographic Report

Upon opening the App, patients are presented with a human silhouette displaying the location and current size of every tumor as well as a graph showing the change in size of each tumor over the course of treatment. If a patient only has a baseline scan, and has yet to start therapy, the software will show the size and location of every tumor. At each follow up visit the tumor size on the silhouette will change to reflect the new findings (Figure 1, link to video). The oncologist can use the patient-friendly radiographic report to explain to the patient how their tumors are responding to therapy. Further, the oncologist can explain to the patient why a change in therapy is being recommended (or not). At present, data will need to be entered into a spreadsheet which is then loaded into the software. Future versions may use direct input (click and enter size/dates/location) with dropdown menus, AI reading of traditional radiologic reports, or AI analysis of the raw scans directly linked to the software.

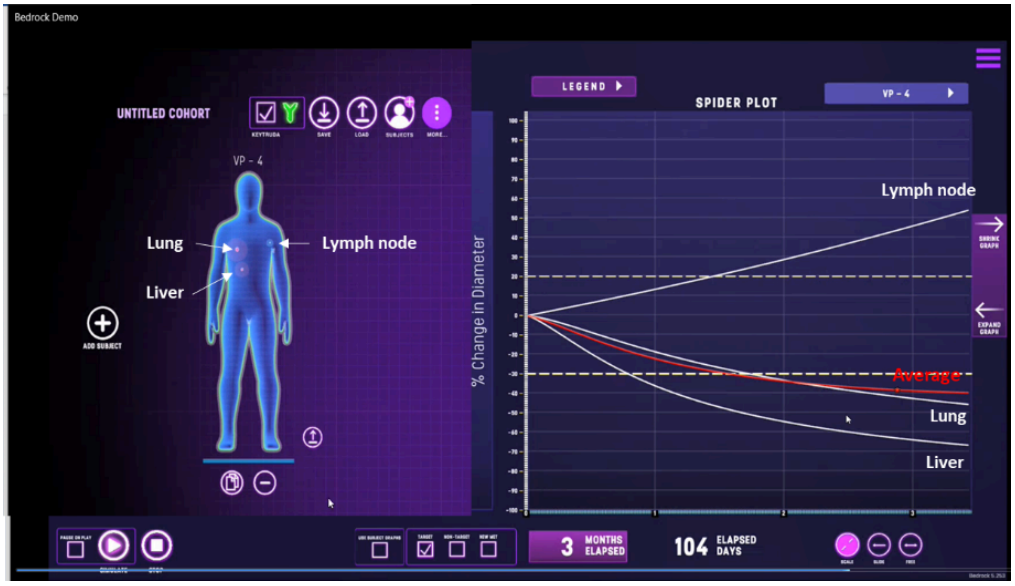


Figure 1 A screenshot of the bedrock software showing a patient with three tumors. Two are shrinking but the third is growing. This visualization allows the physician to clearly explain the mixed response to treatment and to explain why a change in treatment may be necessary (such as the addition of radiation to just the growing tumor). Link to video -- https://youtu.be/cFvW3Kp_Fdw

The Oncologists Dashboard

When a health-care provider opens the app, a silhouette for multiple patients pops up (Figure 2). This can be all the patients that the oncologist is going to see that day, or it can be every patient that are in the oncologist's care. The oncologist can click on any one patient and move to a patient level screen (described above). Prior to meeting with the patients, the oncologist can review the latest data for each patient and decide on what recommendations would be appropriate for each patient. At present, data from the central lab is converted into a spreadsheet with the pertinent data and loaded into the software. Future versions may establish a direct link to the database or utilize AI to both read and visualize the scan results. Future versions may also include a direct link to the radiologic report and/or images.

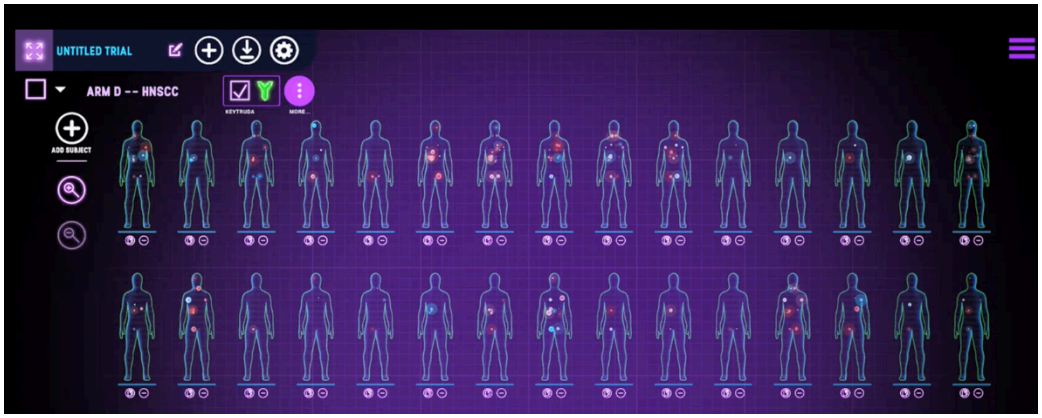


Figure 2 A screenshot of the oncologist's dashboard. Here we see a representation of each patient under the oncologist's care. Clicking on a silhouette of a patient brings up a visualization of patient's individual lesion response to treatment. Future models will include additional medical information on individual patients.

At present the model is limited to individual lesion data, but it can be easily modified to include addition information such as patient demographics, disease history, present/past therapy, adverse events, biomarker data, or other medical information. This rapid visualization for each patient may make decision making faster and potentially better. For example, patients with RECISTv1.1 disease progression are often advanced to the next line of therapy (discontinue current therapy and switch to a new therapy). However, patients with oligoprogression may benefit from remaining on the current therapy (to address the responding lesions) while adding an additional line of therapy can be started (to address the growing lesions). This could, in theory, slow progression through the available lines of therapy and push back the time when all options have been exhausted.

An Oncology Clinical Trial Tracker

Upon opening the clinical trial tracker, the user is presented multiple digital twins (defined here as a virtual representation of the tumor dynamics observed in real patients), similar to the MDs dashboard. Each twin displays the proper location and size for every lesion for an actual patient in the trial (Figure 2). The user can then press run and visualize individual lesion dynamics for a single patient or sum of diameter data for cohorts of patients (ex. spaghetti plots or waterfall plots). Other graphs such as progression free survival or overall survival are also available (Figure 3). While the present model only visualizes tumor dynamics and RECISTv1.1 score, it can be modified to include other data such as biomarker or pharmacokinetic data. This would allow the user to see if responding patients are biomarker positive or if progressing patients are positive for anti-drug antibodies (ADA). The user can then switch from single cohort view to the multiple cohort clinical trial view and compare the cohorts (ex. placebo, active control, historic data, competitor data). Again, the model only visualizes tumor dynamics at this point, but it can be easily modified to include other historical clinical data of interest or algorithms (such as bootstrapping) to compare data across cohorts or correct for meaningful covariates that differ between cohorts.

Figure 3 A screenshot of the clinical trial tracker in Bedrock. Here the researcher can easily pull up standard graphs, such as spaghetti plots, waterfall plots, and Progression Free Survival plots, for any clinical cohort. The researchers can also compare across cohorts or to historical control data. Link to video – https://youtu.be/8IO5uuuYfWs

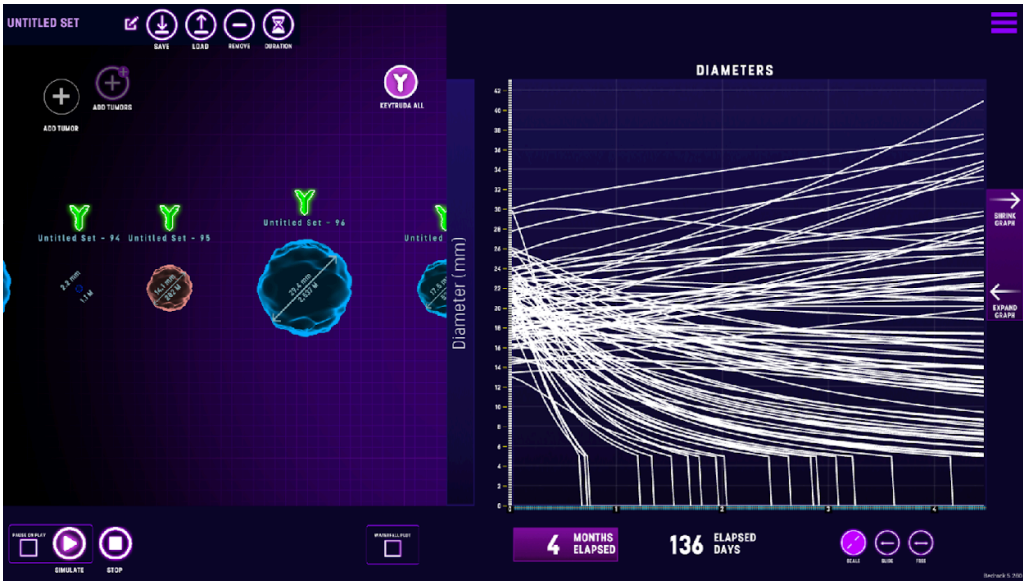
A User-Friendly Immune-Oncology Simulator

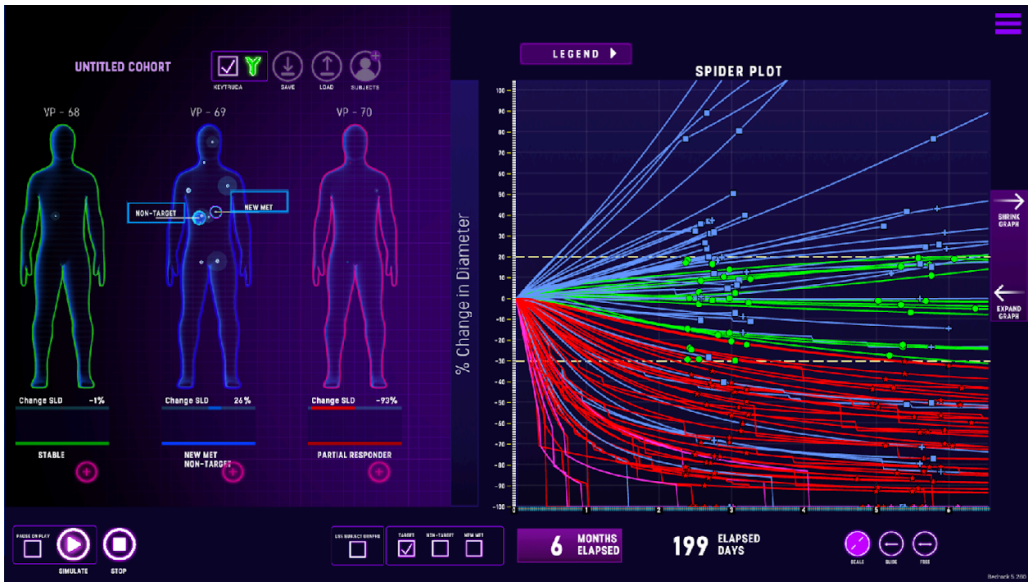
The Immune-Oncology Quantitative Systems Pharmacology module has three sections. Virtual tumors, virtual patients, and virtual trials. The user can intuitively create tumors with various size, growth rate, cytotoxic lymphocyte density, T-helper cell density, and T-regulatory cell density. Future versions of the software may include additional physiology and biomarkers. It is also possible to automatically create hundreds of tumors simply by entering the mean and standard deviation for each controllable parameter then choosing the number of tumors that you want to create. Pre-specified tumor sets exist that have been calibrated to specific datasets from the literature (for example, metastatic melanoma based on data from the Keynote-001 study). From here the user can turn on/off therapies of interest. The model includes pembrolizumab as a default therapy, but new therapies can be added to the model. The user can then simulate systemic therapy and visualize the responses of the individual lesions or groups the lesions (Figure 4A).

The virtual patient section allows the user to create patients by dragging tumors from specific organs onto a virtual patient. Tumors can be set as Target or Non-Target for calculation of RECISTv1.1 scores. Cohorts of various sizes can be automatically created based on mean/variance of tumor pathophysiology, variance in the number of tumors per patient and the location of tumors. Therapies can be turned on and simulation can be run. The software calculates the probability of developing a new metastatic lesion, for each patient at each point in time. Standard graphs such as tumor dynamics (individual or sum or diameters), waterfall plots, progression free survival plots can be intuitively generated (Figure 4B). The software can be easily updated to include subplots based on demographics, pathophysiology, biomarker, PK or other data. Simulations can be used to project the probability of technical success, identify responder populations, and/or optimize trial design.

The virtual clinical trial section allows the QSP modeler to set up and simulate clinical trials of any size (Phase I, II, or III), in any of the pre-determined cancer populations (ex. melanoma, NSCLC, etc.). The trials can be set up as randomized controlled studies or single-arm studies. At present the model can simulate pembrolizumab and placebo. The software can be modified to include additional therapies. Single arm studies can be compared to pre-determined historic control data (loaded into the software). All the graphing capabilities from the virtual patient

section are available in the virtual clinical trial section. In addition, the mean and variance from each arm can be compared against each other for each of the standard oncology plots (Figure 4C).





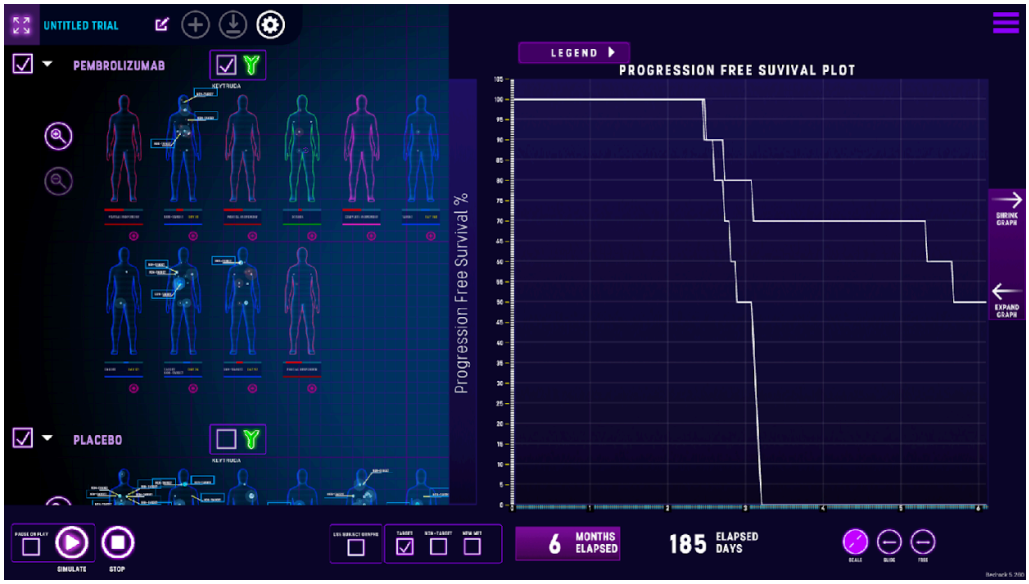
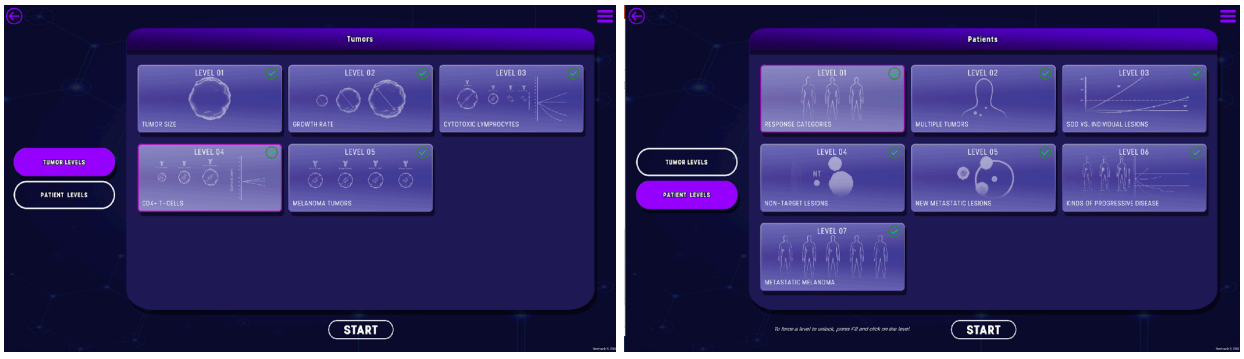


Figure 4A, B, C Screenshots of the Bedrock Physiologic-Based Simulation Platform. (A) shows highlights the ability of a user to create individual tumors with very specific pathophysiology and test their response to treatment. (B) highlights the ability of the researchers to create cohorts of virtual patients with realistic pathophysiology and predict clinical outcomes for novel therapies. (C) highlights the ability of the user to compare across cohorts treated with different drugs. Link to video – https://youtu.be/zmGbmGm5zzk

A Next Generation Oncology Textbook

The interactive textbook section opens to a series of lessons that explain the basics of clinical oncology. This includes mean and range for tumor size, distribution of tumors from organ to organ, tumor growth rates, and characterization of the immune microenvironment (Figure 5A). This is followed by a section detailing lesion-to-lesion heterogeneity, the appearance of new lesions, and RECISTv1.1 scoring of response to therapy (Figure 5B). This section provides self-directed learning. Following the lessons, the student should be able to go to the sandbox and build realistic tumors and patients. The software can be modified to include challenge questions that simulate clinical practice (ex. a patient presents with the following symptoms, what is your diagnosis and recommended therapy). Different versions of the interactive textbook can be made for students of differing levels and perhaps even a patient-friendly summary oncology basics.



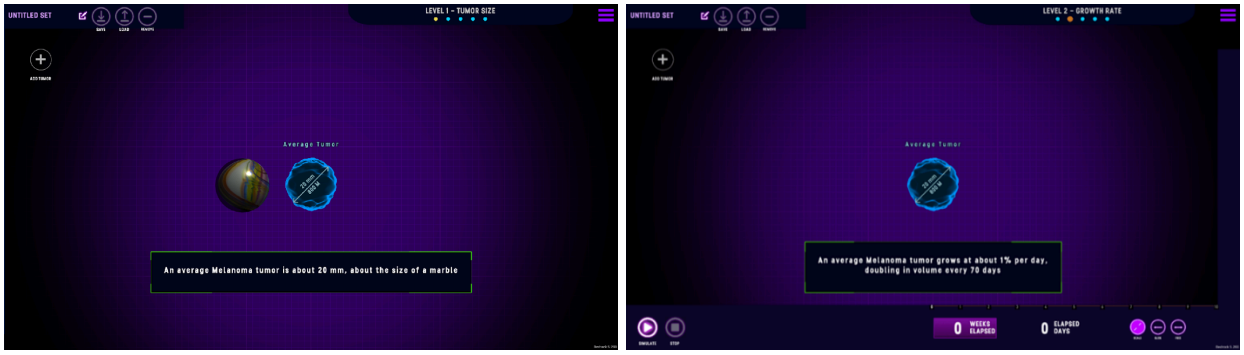


Figure 5A, B Screen-Shots of Bedrock Virtual Professor

Discussion

Here we present a tumor visualization software that is intuitive, interactive, and engaging. We believe that this tool can empower patients, help oncologists be more efficient, enable researchers to both predict and analyze clinical trials, and facilitate learning by students and patients. More importantly, we believe that this tool can facilitate and improve discussions with patients during clinical consultation and with multidisciplinary treatment teams.

Cancer patients are increasingly interested in access to their scan results (CT, MRI, PET)[7]. A recent study of 53,277 patients showed that cancer patients requested their radiology report be placed on the patient-portal more often than any other medical document[25]. A different study of 130,000 patients showed a majority of patients accessing the radiology report on the portal, despite challenges in understanding the document[26]. Other studies have shown that patients would like access to the full radiology report, and they would like to access it as soon as possible on a portal[22]. Patients have also expressed interest in seeing actual images of their tumors, even though they have a limited ability to interpret these scans[23]. Finally, a recent study showed that patients with access to imaging results participated in their medical decision making and showed better outcomes than patients that did not access radiologic data[24].

While the medical community has made great strides at providing access to radiology reports, these reports are all too often incomprehensible to patients[3], the most common complaint being unclear of technical language[28]. While some effort has been put into increasing patient health literacy, (providing definitions and explanations of technical terms), most efforts have focused on providing simpler explanations of radiologic findings[29]. Several authors have proposed structured reports that provide a plain language summary of key findings and clear actionable recommendations[29]. In addition to plain language summaries, there is increasing evidence that visual communication methods can be very effective[30]. To this end, several private companies have developed software/apps that provide a combination of plain language and visual information to help patients understand their radiologic reports[27]. Other efforts include interactive reports with links to pertinent information and video reports from the radiologist[31]. This includes the creation of a Commission on Patient and Family Centered Care (CPFCC) by the American Collage of Radiologist[32]. Finally, it should be noted that oncologists have limited time to assess and communicate complex radiologic information to patients. Several studies

have shown that the use of pictures and graphs (multi-media) can both save time and improve comprehension[27].

Most hospitals maintain radiographic data in the form of radiographic images and radiographic reports. This provides great challenges to researchers investigating real world outcomes[33]. Moving to a system where tumors are measured and entered into a central database (digital radiographic report) would vastly increase our ability to perform real world studies. The generation of gigantic real-world databases that could be interrogated by AI and machine learning systems would potentially be revolutionary.

In most clinical studies, data is stored in huge spreadsheets, then converted into graphs and summary tables via thousands of lines of code. Here we develop a software that can visualize clinical data in an intuitive and interactive manner. In addition, this app provides visualization of lesion-level results that have been historically overlooked. However, as focus on heterogeneity and lesion-level analysis increases across the clinical trial space, this software provides an optimal approach for integrating heterogeneity into clinical decision making. While the first-generation model focuses on tumor dynamics, it would be simple to add pharmacokinetic, anti-drug antibody, biomarker, and adverse event data to allow for a simple and intuitive method of integrating clinical and translational data. Finally, this software provides a simple visual method for monitoring clinical trial progress in real time (ex. how many patients have enrolled, been dosed, responded, dropped out, developed new metastatic lesions, developed AEs etc.).

Systems pharmacology is becoming increasingly common in drug discovery and development. These models have shown value in multiple aspects of drug discovery/development including prioritizing targets, identifying responders populations, identifying optimal combination therapies, and improving dose selection[14,34,35]. However, these models are generally difficult to use and difficult to understand. There are several public QSP models designed to simulate novel immune-oncology drugs[36,37]. While some of these models have developed first generation graphical user interfaces to make their use more interactive and their results more intuitive[16,37,]; the vast majority of QSP models are composed of thousands of lines of code that is completely inaccessible to the clinical researchers that need to understand the models in order to make decisions based on their outcome. Here we developed the data visualization tool that makes QSP modeling intuitive, interactive, and accessible users without coding skills. Further, this software is the first to incorporate tumor-to-tumor variability as well as the probability of developing new metastatic lesions.

Finally, we have developed an interactive textbook that allows students and patients to engage in the learning experience. There are interactive lessons and a sandbox that allows the student to create complex and realistic virtual cancer patients then observe their response to therapy. This is similar to "serious games" being used to train surgical interns or emergency room physicians[(38,39)]. While non-surgical oncology has yet to fully embrace gamification of education, there are some early efforts in this space such as Cancer Crusader and Cancer Sim[(40,41)]. While these efforts generally focus on tumor pathophysiology, we feel that our software provides a clinical and trial level perspective (such as RECIST scores, waterfall plots, and lesion-to-lesion heterogeneity).

Future steps should include an evaluation of the software's impact by analyzing patient outcomes, as well as the efficiency of physician decision-making, particularly concerning therapy selection and modification. Although potential benefits are highlighted, the incorporation of real-world

data or case studies would significantly enhance the credibility of these claims. We should also evaluate its compatibility with the EHR system to avoid duplication of work and to ensure ease of access to patient data.

There is a substantial literature describing the use of visualization to effectively communicate complicated messages[42]. These learning can be incorporated into future versions of the model. While communicating with patients, absolute risk is more effective than relative risk. For example, if two therapies have a similar probability of long-term survival (2% vs 4% for example) a picture showing 2/100 silhouettes shaded red vs. 4/100 silhouettes shaded red provides a patient with a better understanding of risk than saying that the probability of survival doubles by choosing the second drug. When presenting data to scientists, we can improve waterfall and spaghetti plots by showing uncertainties and introducing relevant comparators. Comparing early clinical trial data to historical control arms or the present standard of control provides context not generally shown for tumor dynamics.

Ensuring the privacy of patient information is critical. The tool/app that we developed should comply with healthcare regulations that govern the handling of personal health information. This requires robust encryption and access control measures. Protecting patient data is a critical challenge. The platform will be improved to have strong cybersecurity measures in place to defend against hacking, data theft, or loss. This also includes reliable data backup and recovery systems. Data sharing across research institutions and systems can be hindered by interoperability issues, making it difficult to provide a comprehensive view of patient history and care, particularly when patients see multiple clinicians across institutes. For oncologists or cancer researchers, it would become hard to assemble patient response information through this software if it is not interoperable across systems.

In conclusion, we believe that we have developed a practical tool that could be a gamechanger in the way that oncology will be practiced in the future. The tool offers easily understandable information for patients who can visualize their tumor dynamics in space and time, leading to a more meaningful discussion with their medical team regarding treatment decisions. It will also help oncologists and trialist to have a comprehensive and seamless visualization of the integrated data hopefully leading to a better and swifter patient management. The software provides and interactive textbook companion, essential for modern teaching and education of the next generation clinicians.

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