Can computational modeling help in personalizing the care of patients with pancreatic ductal adenocarcinoma?

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Pancreatic cancer is currently the third leading cause of cancer-related death, and carries a grim prognosis with 5-year survival of only 8% (1). Despite extensive research there has been minimal improvement in the survival of these patients, with an estimate that this cancer will become the second leading cause of cancer related death by 2030 (2). In recent decades advancements have been made in better understanding of the biology of this disease and in the use of combination chemotherapy in advanced disease (3). However, this progress has not translated into significant improvement in overall survival, despite many clinical trials that have been conducted in this arena. Rahib *et al.* evaluated these studies in an attempt to identify benchmarks that could help predict success of clinical trial efforts (4). They identified 32 large phase III studies with a total of 13,675 patients which resulted in only three agents or combinations that were thought to be clinically meaningful. These data highlight the need for revision in our clinical trials design and the need for new research approaches in this disease.

Beyond the overarching poor prognosis that this cancer carries, there is some heterogeneity among patients, clinical presentations, and response to therapy. Two unique classes of pancreatic cancers are well known to have a different pattern of treatment response: (I) tumors in carriers of germline *BRCA1/2* mutations and (II) microsatellite instability high (MSI-high) tumors. As such, *BRCA1/2* carriers with pancreatic cancer have been shown to have pronounced response to platinum-based therapy (5). Furthermore, these tumors have shown response to treatment with PARP inhibitors such as olaparib (6). Albeit a very small

group of patients, those patients with MSI-high pancreatic cancers have a favorable response to immunotherapy with checkpoint inhibitors (7,8). Aside from these two subset of patients the oncologic community is still struggling to achieve better prognostication of patients with pancreatic cancer, and more accurate personalization of treatment.

While majority of patients present with metastatic disease at diagnosis, about 20–30% present with localized disease that may be resectable. The prognosis of those patients with resectable disease is known to be better with 5-year survival in the range of 20% (9-11). Within this group of patients there is a small population of patients with low-volume metastatic disease at presentation or following a curative resection. Limited data demonstrates a potential benefit of surgical resection in this highly selected group of patients, mostly coming from small single institutional studies (12). This therapeutic approach is not considered the standard of care, and thus not recommended by available guidelines (13). A valid biomarker that can aid clinicians in selecting these patients is not available at this time, however, recent studies have started to evaluate the unique molecular profile of these tumors (14,15). Due to the small number of pancreatic cancer patients with this clinical presentation a randomized clinical trial to prove the utility of resection in this population is unlikely to be completed.

The article by Yamamoto *et al.* attempts to explore the feasibility of using computational modeling as a tool to improve the personalized management of pancreatic adenocarcinoma patients with specific attention to the small group of patients with oligometastatic disease. The model was carefully validated in two independent

clinical cohorts, adding to the strength of this work. This computational model is unique in the incorporation of genetic alterations that occur in key driver genes which contribute to the pathophysiology of this cancer. Mutations in *KRAS*, *CDKN2A*, *TP53* and *SMAD4* were included in this analysis as they were previously explored as drivers of disease progression (16,17). The group developed their computational model such that the tumor initiating cells harbors the *KRAS* mutation, and additional mutations develop as the tumor progresses. The authors demonstrate the ability of this model to predict survival which was similar to the survival reported in the two independent clinical cohorts. The model also analyzed survival based on the presence of oligometastatic versus wide spread disease, demonstrating good correlation between survival prediction by the model and those seen in the clinical datasets. Further analysis revealed that this model was able to depict similar distribution of cases in terms of tumor size and number of metastatic sites in both the computational model and the clinical cohorts. In summary, the authors elegantly demonstrate the ability of their model to reproduce the progression of pancreatic cancer as recorded in clinical practice of two different regions around the world.

The model was further used to better define the subset of patients with oligometastatic disease. Within this model such patients had a lower number of cells with two genetic alterations (ALT_{two}) as compared to patients with wildly metastatic disease. This data was used to develop a computational clinical trial in which patients were classified based on the number of ALT_{two} cells ($\geq 10^8$ or $<10^8$ cells). In this theoretical trial patients were randomized to adjuvant chemotherapy versus adjuvant chemoradiation following curative resection. The analysis demonstrated the beneficial effect of adjuvant chemoradiation in the subset of patients with low number of ALT_{two} cells. This trend was also observed when applied to neoadjuvant therapy with chemoradiation. Similarly, this model was used to develop a computational clinical trial to assess the benefit of surgical resection of oligometastatic disease stratifying patients by the number of ALT_{two} cells and randomizing them to chemotherapy, chemoradiation or local resection. The results demonstrated improved overall survival with surgical resection or chemoradiation, only in the group of patients with low number of ALT_{two} cells. In summary, the data supports the use of adjuvant chemoradiation, as well as local resections or salvage chemoradiation of an isolated recurrent site in a specific group of patients with oligometastatic disease and certain genetic profile.

In the above study the authors focused on four "driver" genes that commonly harbor mutations in pancreatic cancer [*KRAS*, *CDKN2A* (p16), *TP53* and *SMAD4*]. Furthermore, their model takes into account the sequence of development of these mutation within the pancreatic cancer cell with *KRAS* mutation occurring in early stage followed by alteration in the other three genes at later stages of the disease. Although these mutations are the ones seen most frequently in this tumor, we currently lack drugs that target them therapeutically. Utilizing the ground work set by this model to develop a mathematical model that includes rare yet targetable mutations with therapeutic effect is warranted. With collection of large amount of genomic sequencing data, it is clear today that the genetic landscape of pancreatic adenocarcinoma consistent of small number of frequently mutated genes followed by multiple genes that are infrequently mutated (17,18). In recent years multiple groups have attempted to classify pancreatic cancer by distinct molecular signatures, yet these classifications have not yet been able to guide the clinical approach (18-20). However multiple research efforts around the world are trying to hone in on the genetic profile and use it to promote pre-clinical and clinical development of novel targets. One such platform is the "PRECISION-Promise" initiative by the Pancreatic Cancer Action Network (PanCan) in the Unites States that aims to coordinate pre-clinical drug discovery and patient specific treatment approaches.

The model described by Yamamoto and colleagues focuses on mutation development within a single cell. There is clear value to evaluation of single cells within the tumor in order to better understand the heterogeneity across the cancer and improve the understanding of the tumor biology (21). Insight into the tumor heterogeneity will allow us to better understand intercellular pathways, and mechanisms that influence disease progression. Furthermore, this knowledge will improve our ability to tailor therapy and insure its effect on all the cells within the tumor. The development of platforms that would allow single cell analysis is underway as well as efforts to move this research tool into clinical practice. Using computational models such as the one in this study along with novel single cell analysis platforms could further our understanding of pancreatic cancer, and open the door for more innovative therapies.

All together, this study demonstrates the feasibility of using mathematical models to analyze clinical features and disease outcomes as well as develop innovative methods to study a unique small group of patients. Using such tools

may enable us to identify factors that distinguish patients' therapeutic response and identify those that would benefit from non-standard treatments. In the current era in which the use of big-data is rapidly expanding as a tool to study cancer while considering multiple factors including: genetics, biology, environmental exposure, treatment, and many more, we are likely to see more studies such as the one published by Yamamoto *et al.* The Blue-Ribbon Panel as part of the Cancer Moonshot Act published an opinion paper summarizing their road map for implementation this form of research calling for harnessing of the power of big-data in innovative simulation and modeling studies to guide practice (22). Big-data has been used to study real-world treatment patterns and patients' outcomes, yet its use for modeling, and for simulation of clinical trials is still in its infancy. This type of initiative will allow for efficient, cost-effective analysis with prompt results that would decrease the need for large clinical trials. Furthermore, the technological ability to encompass large number of variables into the mathematical model in this form of research, allows for the development of a more precise and accurate studies. Finally, given the heterogeneity of each cancer, using this approach can allow for studying a very small unique group of patients that may otherwise require large amount of resources for the conduct of a traditional clinical trial.

Clinical research in pancreatic cancer carries many challenges including the tumor's anatomical location which may limit tissue acquisition and the aggressiveness of this malignancy which does not allow for any delay in treatment initiation and thus may limit the patient's enrollment on studies. As we continue to engage in extensive pre-clinical as well as clinical research with the goal to improve the survival of patients with pancreatic cancer we must consider alternative research strategies such as the one outlined in this manuscript. The use of mathematical modeling to analyze data and conduct theoretical clinical trials could serve as a robust tool that can be used to guide actual clinical trials design and optimize utilization of resources and patients' participation in clinical research. As these types of models are refined, development of a user friendly graphic interaction tool based on mathematical modeling should be evaluated prospectively to better assess its clinical utility. Yamamoto and colleagues should be commended on leading the way in this innovative research methodology.

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Footnote

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