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Archives of Cancer Biology and Therapy Commentary

The Challenge of Cognitive Dissonance in the Delivery of Precision Medicine in Veterinary Oncology

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The use of molecular and genomic analysis of a cancer as a means to define a patient-specific treatment is interchangeably referred to as Precision Medicine, Personalized Medicine, or Genomically-directed medicine (herein, collectively PMED). In the foregoing commentary we have focused on PMED approaches related to treatment selection and do not prioritize the development of novel molecular assays used to guide patient diagnostics or prognostication. At every step in the delivery PMED as an innovative and complex approach to guide selection of treatments for patients, new knowledge and awareness is uncovering gaps in the PMED field, that when addressed will allow PMED to be more broadly applied across cancer types for both human and veterinary cancer patients. The speed of change in this field is dramatic and includes the resolution of prior gaps, almost as quickly as new gaps become understood. Despite this rapid advancement of the field, the current level of evidence for value of PMED in veterinary patients is very limited. We nonetheless believe that as these gaps are resolved and solutions published with transparency that PMED will be part of the future of veterinary cancer medicine. As is the case for human patients, adoption of this approach to cancer care in veterinary oncology will not be uniform, with some patients and clinicians seeking this approach sooner than others.

Recognizing the Scientific Dissonance of PMED

Non-uniform adoption of innovation is common, especially when the value of an innovation is differentially understood and appreciated by distinct audiences in the market. In the setting of this discussion on PMED, we define value as improvements in patient outcome derived from therapy or meaningful new knowledge that inform client communication and decision-making. An important reason for the greater non-uniform adoption observed with PMED is the cognitive dissonance surrounding the field. On one-hand, it is largely agreed that cancer is a disease of dysregulated genes. On the other hand, a therapeutic advantage from a knowledge of these dysregulated genes remains surprisingly difficult to demonstrate. A balanced perspective on the human field suggests that value from PMED is currently limited to a small spectrum of cancer diagnoses and a similar narrow set of evaluated PMED platforms.

A cognitive dissonance develops when a person holds two beliefs that are contradictory or inconsistent. In this case, oncology clinicians understand that cancer is a disease of dysregulated genes. Accordingly, it is reasonable to conclude that advancing our knowledge about specific dysregulated genes in a tumor should allow us to better select drugs and improve patient outcomes, rather than merely "guessing" based on tumor histology and clinical data/experience. However, the evidence from studies in the human PMED field, particularly when applied across tumor types, do not yield this expected value compared to "guessing" [1,2]. How could it be that having more information results in no valuable improvements?

The sources of this cognitive dissonance are explained by many of the remaining gaps in the field. The allure to conclude that a greater understanding of cancer genomes will lead to improvements in patient outcome combined with the "race to zero" on cost for genomic testing creates an imperative to recognize the dissonance and its underlying gaps, since new innovations are entering the commercial veterinary market. The result of this

new commercialization is an expected friction between those who can offer innovations in PMED now, against the variable needs for evidence and value desired by pet owners and clinicians. The urgency to commercialize what can be done is understood; however, the risks of delivering innovations that do not add value should also be understood both from the cost of the product that fails to meet expectations of the innovator and the broader cost to the future desired adoption of PMED in veterinary oncology.

Communicating This Scientific Dissonance

Ultimately this cognitive dissonance must be understood and managed by clinicians as they play the important and expected role as "honest-broker" with the often "vulnerable" family of a pet animal with a cancer diagnosis. The responsibility of "honest broker", is not taken lightly by most veterinarians especially in the field of reference lab diagnostics for companion animals, where there is no outside regulatory body playing this role prior to commercialization. Not surprisingly this is exacerbated by the fact that a broad segment of the veterinary clinician community does not have the background to easily recognize the existing gaps and the evidence needed to fill the gaps. Therefore, an open dialogue on the value of PMED is needed. Furthermore, the visibility of PMED to the lay public makes the pet owner equally susceptible to this same dissonance. A necessary and simple starting point in this unregulated landscape is a reasonable request for innovators to publish the following peer-reviewed data: (1) the performance of their assay in relevant settings (2) experience with any recommended drug emerging from a PMED analysis in pet animals with cancer prior to that drug's recommendation, and (3) to deliver evidence of the value of their PMED offering through robust prospective clinical studies. The timing of these peer-reviewed publications and commercialization is expected to become a differentiator amongst innovators. Such a request for publication and transparency is much less burdensome and more desirable to clinicians than required for the approval of veterinary drugs and is a starting point for PMED innovations in veterinary medicine.

What is the Alternative for Patients in Need?

It is recognized that the process of publication and transparency is time consuming and will delay the availability of a PMED innovations to a patient in need of new options, now. Novel therapeutics offered through rigorous clinical trials can be offered to patients in need of new options now, without PMED. Indeed, the biological rationale to open trials with well-considered eligibility criteria under appropriate clinical trial standards is sufficient to recommend clinical trials of new drugs to pet owners in need of new options for their pet. As stated above there are currently narrow instances, even in the human, where a PMED selection (i.e., matching) of patients to new drugs in a clinical trial has delivered significant value to the patient compared to the clinicians best medical judgement, hence today's patients in need should be offered clinical trials. Furthermore, data from these trials may address existing gaps in PMED delivery to veterinary patients though a contextual understanding of the drug in question (as discussed below).

What are the Largest Remaining PMED Gaps?

Challenges to the field of precision medicine must be addressed before this important and novel approach to cancer therapy will improve outcomes, in the commonly preferred pan-cancer strategies, deployed by some innovators. These approaches recommend a single PMED platform to be used for all cancer diagnoses. The following scientific gaps that must be addressed to deliver value from PMED include but are not limited to the following:

1. Understanding therapeutic/biologic context

Before simply matching drugs to genomic events, we must study and develop an understanding of the biologic context of these genomic events, vis a vis, tumor biology and therapeutic responses. We have learned that the behavior and outcome of therapeutically targeting of a given molecular alteration in a cancer is best defined in a given cancer and may not extend to the same alteration in a distinct cancer. For example, the presence of a BRAF V600E mutation in human melanoma, when targeted with an appropriately tested RAF inhibitor, yields valuable treatment responses for patients. Somewhat surprisingly, the identical mutation found in human colon cancer treated with an identical RAF inhibitor yields no similar treatment benefit [3]. There are accompanying genomic alterations that may explain this result in some cancers; however, it is reasonable to expect that such genomic explanations will not be found or will not be the same in every cancer (i.e., biological context will be tumor/context-specific and will not likely be resolved by more genomic data alone). Interestingly, canine bladder cancer (transitional cell carcinoma) has been found to express a canine version of this BRAF mutation. It should be even less surprising that the biological context will not be shared across species. Therefore, an understanding of the value of a specific RAF inhibitor in dogs will be needed before the instinct to match a BRAF mutation with a RAF inhibitor in canine bladder cancer will deliver a benefit. Fortunately, such studies are underway by several groups working with these inhibitors and canine bladder cancer. Resolving biological context in a disease- specific manner can include a daunting set of preclinical and cell-based studies using gene knock- out

and knock-in technology, but as demonstrated in recent human PMED trials this question of biological context can be as simple as understanding the clinical activity of novel drugs in early phase clinical trials in the cancers of interest. Ideally these early phase trials will include appropriate PK/PD (pharmacokinetic/pharmacodynamic) analysis. In the human PMED experience, when the understanding of a drug in the context of a specific cancer has been defined, the value of PMED in human patients is more clear.

2. Cancer heterogeneity - evolution

Of the many sources of cancer heterogeneity, the heterogeneity associated with disease progression (often described as cancer evolution) may be most problematic to PMED [4]. For many patients, the presenting tumor is resected and the greatest risk to that patient results from recurrence of that resected tumor or spread to distant sites (i.e. metastasis). Accordingly, in many cancers, it is likely most helpful to understand the genomic underpinnings of the recurrent cancer or the disseminated microscopic cells that will lead to metastasis than the genomics of the primary and resected tumor. Accordingly, either a more contemporaneous biopsy is needed for PMED analysis of a patient with recurrent or metastatic cancer, or validated assays of circulating cell-free tumor DNA, used as a surrogate of the disseminated tumor cells, must be developed as an alternative substrate for PMED (i.e., as part of a liquid biopsy approach). Contemporaneous biopsy material is increasingly mandated in most new human PMED trials. Although currently disappointing, circulating cell-free tumor DNA analysis for drug-matching is the topic of intense research activity. It is likely that a circulating cell-free tumor DNA analysis approach in a specific cancer will be validated and become the preferred surrogate material for future PMED approaches for this reason.

3. Cancer heterogeneity - geography

A distinct form of cancer heterogeneity that is equally problematic to PMED involves substantive differences in the number and nature of genomic alterations in distinct regions of a tumor [5-8]. The magnitude of geographic heterogeneity is known to vary by cancer. In those cancers where geographic heterogeneity is high, additional understanding of genomic driver and passenger events is needed. Otherwise tumor-specific approaches will be needed to sample a patient's tumor so that more informative regions of a tumor are included in the PMED analysis. Furthermore, sampling of multiple sites within a primary tumor are needed to provide a better understanding of genomic events and the presence of specific driver mutations for drug targeting [8-10]. As described above, based on the presumption that important genomic events will disproportionately persist in a patient, innovations in liquid biopsy approaches that allow validation of circulating cell-free tumor DNA as a surrogate of the most informative geographic regions of a tumor may also represent a solution to this problem.

4. Aligning PMED platforms with specific cancer use cases

There are a variety of PMED platforms available for both veterinary and human patients. Some platforms may be best suited to specific cancer use cases (i.e., clinician questions). For example, transcriptomic signatures may best define optimal selection of conventional chemotherapy. Next generation sequencing approaches may be best used to identify novel salvage therapies for advanced cancers. In addition to the platform, the drug-matching algorithms are also distinct and require validation. It is unlikely that a single platform/algorithm will provide answers to all cancer use cases. Despite current commercial priorities to build pan- cancer solutions for PMED, it is more likely that PMED strategies will be successfully validated within a specific cancer setting. Such an approach will be a less scientifically risky and deliver value to patients more quickly.

5. Platform complexity. Is it as simple as the gene?

It is unlikely that a single platform/algorithm will provide answers to all use cases despite efforts to build an all cancer solution. Furthermore, the dysregulated genes in a cancer may be better understood by studying non-genomic [11] and non-coding events [12,13]. The cancer epigenome is a substantial source of the dysregulation of genes in cancer. Indeed, the genetic code alone does not fully represent the complexity of cancer as there are many processes and regulatory steps (collectively described as the epigenome) that can be altered and lend to dysregulation of genes. Awareness of the importance of the epigenome further expands the spectrum of PMED platforms that should be considered for optimal care and may be better aligned with some cancers compared to others [13,14]. Finally, since the epigenome may direct cancer progression [15,16], metastasis [17], and drug resistance [18], targeting the epigenome may be useful in a PMED strategy and may uncover more relevant and broad-spectrum targeting approach to more cancer types [19].

6. Canine genome annotation

A veterinary specific challenge to PMED innovations is our incomplete annotation of the canine genome. Basic genomic annotation can allow confidence in naming a gene or a gene mutation accurately in the dog. Annotation can also involve a more complex process of confidently understanding the biological function of that gene in the

dog. Progress on both forms of annotation are underway in the dog [20]; however, the value of PMED in veterinary oncology will be limited until such annotation is more complete. It is important to note that in the field of veterinary oncology, the dog genome is most advanced and most poised for innovations and PMED oncology applications than other veterinary species at this time.

What is the most likely path for effective integration of a PMED approach into the management of the veterinary cancer patient

Why is this future so close, but yet so far away from delivering value to our patients? The unresolved questions surrounding PMED and the study of the successes in the human provide lessons and advice that should be considered by clinicians and innovators desiring similar approaches for veterinary patients. In the era of PMED in the human, the promise is most evident in lung cancer and less clear in "all comer i.e. pan-cancer instances". This one cancer at a time success in human PMED predicts similar success when PMED options are developed, validated, and then delivered to the veterinary market. Clinicians and innovators should be cautious as they develop or consider the use of pan-caner PMED solutions.

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