Commentary

Precision medicine: an opportunity for a paradigm shift in veterinary medicine

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With certain complex medical conditions, it is now both reasonable and feasible to use genomic and other molecular analyses to identify the true drivers underlying the condition and correlative studies to link those drivers to specific treatments.[1] Such an approach has been variably described as personalized medicine or molecularly guided medicine, but the term precision medicine is most often used. Note that the use of terms such as personalized medicine and precision medicine to describe this approach is not meant to suggest that other medical approaches are not personalized or precise. Rather, such usage highlights the greater degree of precision afforded by genomic analysis of individual patients.

Recently, the concept of precision medicine has received broad attention in both human and veterinary medicine and in the scientific and lay press. In addition, during his 2015 State of the Union Address, President Obama announced the launch of a Precision Medicine Initiative to spur research, development, and innovation in the field.[2] For human patients, precision medicine has seen its broadest application in the field of oncology. However, despite the unquestioned value of defining cancer at its molecular level, many questions about the value of this approach remain unanswered, and there has been, to date, limited evidence of improved patient outcomes associated with the precision medicine approach. Rigorous study of the various steps in the precision medicine process would benefit from the development of disease models that capture the patient-to-patient heterogeneity of complex medical problems such as cancer and the heterogeneity of outcomes in patient populations. Because of their unique training and perspective, veterinarians are uniquely positioned to help address gaps in our understanding of precision medicine and the evidence supporting it. This includes all aspects of precision medicine from development of screening and confirmatory diagnostic tests based on results of molecular analyses to identification of molecularly targeted treatments and molecularly guided treatment decisions. The outcome of such leadership from the veterinary profession will be an accelerated understanding of the value of precision medicine for human and veterinary patients and improved delivery of precision medicine approaches.

Precision medicine has the potential to revolutionize the practice of medicine and improve treatment outcomes. While the main focus currently is applications in human medicine, the veterinary profession has much to offer and much to gain. Molecular phenotyping of animal diseases will connect those conditions with similarly characterized human disorders for which precision treatments have been or are being developed. Conversely, the highly homologous genomic structure of domestic species such as purebred dogs constitutes an important advantage in the identification of molecular variants that are causally linked to specific diseases or disease risks. Clinical trials involving human and animal patients with a variety of cancers are increasingly providing information about shared driver mutations that constitute important drug targets. This is an important opportunity for veterinarians and veterinary scientists.

Optimization of the precision medicine approach depends on integrating information on diagnostic and therapeutic approaches through the use of a new taxonomy based on specific molecular biomarkers of disease. The transformative potential of precision medicine is exemplified by ongoing changes in three key areas of clinical oncology: screening and confirmatory diagnostic testing, drug development, and treatment selection.

In the area of diagnostic testing, precision medicine has dramatically improved screening of at-risk individuals through genetic assessments for cancer-

predisposing mutations. Increasingly, patients with a family or personal history of cancer are being tested for mutations in cancer-predisposing genes, and new studies have suggested that expanding genomic assessments through the use of next-generation sequencing can dramatically enhance the power of such screening. As a result of these approaches, new screening guidelines are being developed, with, for instance, the National Comprehensive Cancer Network now recommending expanded cancer gene sequencing for patients with a family history of breast or ovarian cancer who are negative for common hereditary mutations.[3]

Beyond screening, tumors are increasingly being classified on the basis of specific genetic mutations rather than tissue of origin, which may improve both differential diagnosis and patient stratification. The diagnostic yield of genomic analysis has been shown to outperform targeted molecular analysis and, in some cases, may outperform standard pathological examination.[4,5]

With regard to drug development, precision medicine focuses on discovery of small molecules that, by targeting cancer-specific mutations, can potentially expand the therapeutic index of chemotherapy. The first such genomically targeted drug was the selective tyrosine kinase inhibitor imatinib, which was developed to target the *BCR-ABL* fusion gene associated with chronic myelogenous leukemia.[6] Since then, other drugs have been developed to target specific cancers, including epidermal growth factor receptor inhibitors (both tyrosine kinase inhibitors and monoclonal antibodies) used to treat breast and colorectal cancers; sunitinib, which targets mutations of the tyrosine kinase receptor implicated in a variety of cancers (eg, renal cell carcinoma, gastrointestinal stromal tumor, and pancreatic neuroendocrine tumor); gefitinib and erlotinib, which are used to treat lung cancers that have mutations of the epidermal growth factor receptor; crizotinib, which is an anaplastic lymphoma kinase inhibitor used to treat certain lung cancers and neuroblastomas; vismodegib, which is used to treat certain basal-cell carcinomas with mutations of the hedgehog signaling pathway; and vemurafenib, which is a B-Raf enzyme inhibitor used to treat certain melanomas. Many more novel agents targeted to mutant cancer genes are currently undergoing preclinical development or clinical trials involving human or veterinary patients.

Finally, precision medicine is transforming cancer treatment, in that molecularly guided treatments have the potential to provide improved outcomes, compared with nontargeted interventions such as surgery, radiation, and chemotherapy alone. For example, although melanoma[7] is clinically distinct from hairy cell leukemia,[8] they share identical BRAF V600 mutations,[9] and vemurafenib is effective against substantial proportions of both cancer types. Conversely, vemurafenib is ineffective against colorectal cancers that also have EGFR mutations.[10] Similarly, pediatric neuroblastoma and anaplastic large cell lymphoma commonly have ALK mutations, and both can be treated with crizotinib.[11,a]

Many prospective clinical trials are now assessing the hypothesis that precision medicine can improve treatment outcomes in patients with cancers. The first such trial, published in 2010,[12] found that using molecular profiling to guide treatment selection for human patients with refractory metastatic cancers resulted in longer progression-free times in 27% of patients, compared with previous progression-free times for those patients. Numerous other observational and interventional trials have been published or are ongoing, including adaptive trials such as I-SPY 2, in which treatment is adapted on the basis of patient response; basket trials such as the National Cancer Institute's Molecular Analysis for Therapy Choice trial, in which patients with various advanced cancers are assigned to treatment baskets on the basis of mutations identified in their tumor cells; and umbrella trials, in which targeted pharmaceuticals are assessed for efficacy against a single disease.[13–19] This same approach is starting to be used for the diagnosis and treatment of tumors with similar mutations in dogs, although much remains to be learned about the molecular features underlying canine cancers.[20,21]

Of course, even in the context of cancer, genomics is only one of several disease aspects that may have an impact on clinical management. As described, precision medicine can involve identifying genetic variants and matching those variants with specific therapeutic approaches. A more holistic view of precision medicine, however, would include consideration of a wide variety of factors involved in disease development and progression, including personalized assessments of environmental exposures, identification of distinct metabolic pathways, and evaluation of other yet-to-be-identified factors that may be of importance at the patient, herd, or population level. Theoretically, the veterinary profession could rapidly provide evidence to validate this approach, including evidence that arguably has not been provided through human studies alone. For example, observations and measurements made in carefully designed clinical trials of pets with cancer may accelerate the optimization of precision medicine at many levels and inform the use of this approach in human patients with molecularly identical diseases.

In time, precision medicine will likely have an impact not only on cancer treatment but also on treatment of a wide variety of diseases, including diabetes, obesity, and various infectious diseases, that occur in animals and have the same underlying etiology as similar conditions in humans. Precision medicine also promises to have an impact on those diseases in animals for which comparative medical research has as yet had little effect or that are unique to animals. Importantly, for all 10 of the leading causes of death among people in the United States (eg, atherosclerotic heart disease, cerebrovascular disease, Alzheimer disease, and chronic lower respiratory tract disease[22]), a recognized spontaneous counterpart with similar clinical incidence in veterinary patients has not yet been identified. However, as comprehensive omic profiles are generated for people with these conditions, it will be possible to compare these findings with findings of similar analyses performed on pets. The discovery in animals of molecular profiles and biomarkers associ-

ated with distinct clinical presentations will provide new insights into disease mechanisms, pathogenesis, and progression and reveal new candidates for molecularly guided treatments. This precision medicine approach in veterinary patients may not only lead to the development of new diagnostic criteria, therapeutic targets, and prevention strategies but also contribute to improvements in human medical care.

Precision medicine promises benefits to veterinary clinical practice beyond defining disease pathogenesis on the basis of shared molecular mechanisms between humans and animals. The percentage of human patients in which a diagnosis has been made on the basis of clinical signs but for which standard drug treatment is ineffective ranges from 38% to 75%.[23] Although similar clinical data for animals are not readily available, it is reasonable to assume that standard drug treatments used in veterinary medicine will be ineffective in similarly high percentages of animals. Precision medicine offers an opportunity to instead use molecularly guided data and information to deliver the optimal medication in the right amount to the right patient at the right time.

Given the recent opportune convergence of several scientific, technical, and social advances, the time is right for the veterinary profession to take a bigger role in the field of precision medicine. These advances include the dramatic technical and cost improvements in next-generation sequencing and other molecular technologies, the broad application and widespread use of electronic medical records and digital data, the advent of new mobile devices to track individual health, and the development of increasingly sophisticated bioinformatics tools for interpreting large data sets. In addition, today's patients are more ready and willing than ever to engage as active participants in medical research studies that have the potential to benefit them and to partner with doctors and other health-care professionals to help them and their family members (both two-legged and four-legged) live longer and healthier lives. Further, the practice of precision medicine will inform other aspects of medical care, including disease susceptibility, pharmacogenomics, disease surveillance, risk of surgical complications, and development of drug resistance. Overall, precision medicine has the potential to guide more specific diagnostic testing, inform more effective clinical decision-making, and drive more successful treatment interventions.

As a profession based in science and committed to improving animal and human health, veterinary medicine can use the same technological tools, scientific expertise, and social awareness now being used in human medicine to advance the clinical practice of precision medicine. Indeed, as members of the animal-loving public themselves become the beneficiaries of precision medicine, they will begin to ask whether similar, precision-guided approaches to clinical medicine can benefit their animals. To generate the knowledge with which to answer these questions, veterinary medicine will need to make investments to pursue comprehensive molecular-based diagnostic testing, commit to openly share omics data and clinical patient information, and follow through with carefully designed clinical trials of molecularly targeted treatments. It will also require the development and implementation of new strategies to educate and train clinicians, veterinary students, and related health professionals in genomic medicine, bioinformatics, and other key components of the practice of precision medicine. Further, the veterinary profession will need to be cognizant of opportunities that will soon be available for owners to partner in their pet's health. Veterinarians will need to be ready to respond to this new and greater engagement by animal owners.

Results of basic and applied research in the field of precision medicine will undoubtedly reveal more evidence of the extent to which humans and animals share common molecular mechanisms of disease pathogenesis that are clinically relevant and therapeutically actionable. Adopting this new paradigm for enhancing the diagnosis, treatment, and prevention of disease has the potential to dramatically transform the practice of both veterinary and human medicine. As the gaps in our knowledge are overcome, opportunities to meaningfully improve the clinical effectiveness of disease-fighting treatments will increase greatly. In this way, precision medicine is the epitome of one health and will continue to have a transformative impact on the lives of people and animals and the environment they share.

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Footnotes

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