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Editorial

Personalized and One Medicine Coming Together

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In an earlier publication (see for detailed information and references [1]), we highlighted the contributions of new genetic and bioinformatics tools to the development of personalized medicine. We also considered how these developments might be used to accelerate advances and reduce healthcare costs based on the principles of One Medicine.

Personalized medicine focuses on the development and application of therapeutic strategies that are tailored to specific patient characteristics. One successful example of this direction is trastuzumab, which is a humanized monoclonal antibody used to treat patients diagnosed with advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancers. Similarly, cetuximab and panitumumab are monoclonal antibody drugs that have been approved by the United States Food and Drug Administration as targeted treatment of epidermal growth factor-(EGFR) positive metastatic colon cancers.While the introduction of these and related drugs has created a virtual revolution in clinical care, future development of personalized therapies will depend on increased knowledge and understanding of the unique features of each patient and each disease. Ongoing advances will rely on comparatively new and highly sophisticated methods used to explore genome sequences and gene expression both in health and disease states. Among these is whole genome sequencing (WGS), which is a process used to elucidate the sequence and chromosomal localization of the ~3 billion nucleotide pairs in the human genome. While the first near-complete human genome sequence was reported in 2004, several more recent methodologic advances, including whole exome sequencing and single nucleotide polymorphism (SNP) genotyping, have served to advance the field and accelerate discovery. As a group, these tools can be used to identify genetic variation (e.g., polymorphisms and potentially-damaging mutations) and thus may aid in the diagnosis and discovery of genetic diseases and their associated risks. These tools were originally quite time-consuming and prohibitively expensive to perform which precluded their use in routine clinical practice. However, in recent years, some inroads have been made toward using genomic information collected by these methods to develop personalized strategies that address the needs and concerns of physicians and patients.

While WGS and related techniques can provide information on gene structure and sequence, in some cases it may be more critical to evaluate patterns of gene expression. For example, cancers are now frequently classified based on their gene expression patterns rather than their location or tissue of origin. Microarray and RNA sequencing (RNAseq) are two techniques that have been used to evaluate gene expression in specific target cells and tissues. Microarray analysis relies on the quantitative evaluation and interpretation of binding interactions between cellular RNA isolated from target cells of interest and short fragments of nucleic acid sequences (probes) affixed to a surface. This technique has broad application beyond gene expression and is already in clinical use as a means to diagnose viral infections via unbiased detection of viral DNA or RNA genomes. By contrast, RNAseq is a more open-ended and flexible method for evaluating gene expression, as it can be used for simultaneous identification of both characterized and as yet uncharacterized transcripts from multiple sources (e.g., the numerous bacterial species that constitute the human gut microbiome). Both microarray and

RNAseq generate vast amounts of data that require complex statistical evaluation by highly skilled bioinformaticians to generate patterns and clusters useful for further consideration. This has led and will continue to lead to new and more effective and specific therapies for cancer treatment.

While RNAseq remains primarily a research technique at this time, it will eventually enter the mainstream and will be used for clinical decision-making. Thus, physicians will need training so that they will have a clear understanding of this method and thus be capable of interpreting its outcomes.

Given the numerous anthropological, genealogical, and forensic applications of this technology, it is perhaps not surprising that most of the clinical emphasis has been placed on efforts to understand genomic variation and disease-associated gene expression patterns in humans. Thus, while other mammalian genomes have been fully sequenced, the clinical use of personalized strategies in veterinary medicine remains limited. Based on the principles of One Medicine, which is a field that focuses on diagnoses and therapeutic strategies that may be shared by human and veterinary medicine, an improved understanding of genetic variation and its relationship to disease processes in other mammalian species may be an overlooked source of critical clinical information. As a first principle, it is critical to recognize that cellular metabolic and biochemical pathways, growth factors, and signaling mechanisms are similar, if not identical, across many mammalian species. Thus, it is certainly not surprising to find that many diseases (e.g., cancer, diabetes, and arthritis) are frequently diagnosed in both human and animal species.

Future developments in the field of One Medicine will rest on our understanding of conformational matching. Many of our previous publications have highlighted the nature and evolution of structurally-matched ligand-receptor pairs. Based on this principle, we understand that variations will only be tolerated if they can be accommodated within pre-existing patterns. These constraints lead to the overall conservation of critical pathways while permitting the development of novel modalities (e.g., improved cognition).

Finally, recognition and application of the principles of One Medicine may ultimately serve to reduce healthcare costs. Toward this end, we will need to identify methods that facilitate the "retro-matching" of genomic and gene expression data to appropriate clinical pathologies. These and related strategies may provide us with cross-species information that predicts outcomes and adverse events. Taken one step further, genomic and gene expression data from plant species may ultimately be used to understand human nutrition and food intolerance based on our understanding of shared signaling pathways and conformational matching principles. Increased computing capacity and new developments in bioinformatics techniques will ultimately increase the economic feasibility of these directions. Similarly, healthcare costs will be reduced once personalized treatments have been developed that can be used for similar indications in both human and veterinary medicine.

Reference

[1] Stefano GB, Kream RM. Personalized- and One-Medicine: Bioinformatics Foundation in Health and its Economic Feasibility. Med Sci Monit. 2015; 21:201–204.