Perspective

The Role of Pathologist in Precision Medicine

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Abstract: Pathologists will play a key role in precision medicine for the follow reasons. Pathologists have direct access to patient specimens, the most cutting-age diagnostic technologies, and integrated laboratory data to design therapeutic plans. Pathologists also have the upper hand in carrying out translational research utilizing patient specimens. Owing to these advantages, the pathologists will play an important part in future therapeutic target-based and individualized clinical trials, and their role will shift from that of a traditional diagnostician to that of a therapeutic consultant.

The future of precision medicine will rely heavily on the development of precision pathology, which is further determined by the role of pathologists in precision medicine.

Pathologists traditionally diagnose diseases from specimens harvested by clinicians. Clinicians collect specimens from patients and send the specimens to pathology laboratory. Pathologists in the laboratory examine the specimens first with naked eyes. Some preliminary diagnoses can be made by an experienced pathologist in the grossing room based on the observed color, shape, and texture of the lesions. The specimens are then submitted for histological examination to confirm and fine tune the diagnoses. Diagnoses made by pathologists are very straight forward - they describe and classify what they see [1]. As a matter of fact, people often consider pathological diagnosis as the most objective because they think pathologists make diagnoses based solely on what they see in tissues. On the contrary pathologists always integrate clinical information and radiologic findings into their diagnoses. But afterwards, treatment options are largely left with the clinicians and little roles for pathologists.

I used to explain to the general audience about the pathologist's role in patient care by using an example of investigating a criminal case. Primary care physician often gets the first report of the "crime" and radiologist helps to locate the "crime scene". Surgeons as "investigators" go to the "crime scene" to collect evidences. With all the collected evidences presented to her/him, pathologist, being the "judge", will analyze all the evidences (sometimes even conflicting) to rule in or rule out the "criminal(s)". A verdict (final diagnosis) will be made by the pathologist and the "suspects" will be either 'released', 'sentenced' or 'executed' by surgeons and/or hematologists/oncologists.

With development of various biological technologies and artificial intelligence (AI), pathologists know patients much better from the laboratories,

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sometimes even better than seeing the patients by themselves, since most of the genetic makeups and metabolomics would not show at the patient's interviews and/or on physical examinations. With big data and machine learning, pathologists would be able to collect and process tons of information from patients. The information will not only be related to the patient's disease, but also about the patient's physiology, the interaction between the disease and the patient, the interaction between the disease and treatment, and the interaction between the treatment and the patient. Since information can be accumulated with time all through the patient's life, constant interaction between the pathologist and the patient will be the norm. With the first-hand material and the resulted data, pathologists could guide clinicians with treatment plans [2].

There may be disagreement among physicians of different specialties as to their roles in precision medicine, but pathologists have the following major advantages:

1) Pathologists have direct access to patient specimens. Evidence-based medicine relies on objective data produced in the clinical laboratories. Whether being surgical specimens, cytological specimens, body fluids, blood or patient's normal or abnormal discharges, they will be sent to the clinical laboratories and analyzed by various assays. Since pathologists are well trained experts in analyzing these data, they have an advantage in using these patient specimens in the diagnosis, treatment and prognosis of diseases and translational research.

2) Pathologists have access to the cutting-edge diagnostic technologies. Molecular profiling, next generation sequencing, machine learning and AI are more and more widely used in clinical laboratories. Although these advanced technologies can be available in any laboratories, only the CLIA certified pathology laboratories can make clinical diagnosis and only pathologists have access to these diagnostic tools.

3) Pathologists have the first-hand laboratory data on therapeutic targets of disease and patients' phar-

macogenomics, and pharmacometabolomics [3], and with the help of AI analysis they can integrate all these data and design therapeutic plans for managing patients. Clinicians (and/or pharmacists) will manage patients by following pathologists' guidance.

4) With direct access to patient specimens, pathologists have an advantage in carrying out translational medical research, such as biomarker discovery, identification of novel therapeutic targets, and pharmacometabolomics-informed pharmacogenomics [4], etc. The research discoveries can be translated directly into clinical practice.

5) Since precision medicine considers individual variability, clinician-led population-based clinical trials to generalize a therapeutic regimen will eventually give way to therapeutic target-based and individualized clinical trials designed by pathologists.

Owing to the above advantages inherited in pathologists, they will lead the advancement of precision medicine, and thus precision pathology will not only be the basis of precision medicine, but also guide the direction of precision medicine.

Pathologists Remain Morphologists

Pathologists love their microscope because it provides them the morphology of diseases. There were predictions that pathologists and radiologists might be replaced in the future by AI and machine learning [5], which fortunately will not happen. Due to the limitations of AI and complex scenarios in pathology, morphologic pattern recognition will still be an essential task of pathologists. However, in addition to making diagnosis on morphologic examination, pathologists will focus more on the extent of tumor infiltration, recurrence, specimen acquisition and adequacy evaluation for molecular and other ancillary studies. As long as surgery still exists, pathologists will be required to evaluate surgical margins on frozen sections. With the increasing popularity of interventional radiology, pathologists will be needed to evaluate adequacies and to distinguish a *de novo*

from a recurrent disease. Due to the heterogeneity of tumors, results obtained from different parts of a tumor can be significantly different. To acquire accurate information from the tumor, tumor specimens sampled for molecular and other ancillary studies must be from the most representative part of the tumor and only pathologists with excellent training on tumor morphology can take on this responsibility.

Pathologists and Radiologists

As both involved in diagnostic science, pathologist and radiologist play unique roles in precision medicine. As AI will be heavily employed in radiology, image interpretation will be accelerated and promptly reported with almost no delays, which make it possible to skip image interpretation and to immediately perform tissue biopsy if a malignancy is suspected. Perfect collaboration of radiologist and pathologists have already happened between interventional radiologists and cytopathologists. With various molecular tools available, limited amount of tumor cells/tissues obtained by fine-needle aspiration (FNA)/core needle biopsy (CNB) might be able to provide therapeutic targets for treatment of patients prior to a pathological diagnosis. To expedite diagnostic studies, radiology might be combined with pathology in providing diagnostic service to clinicians. A proposal to establish human diagnostic medicine is currently under discussion and cross-disciplinary fellowships may be a daunting practice in the future.

Pathologists Assume Roles in Therapeutic Decision Making

Pathologists traditionally diagnose diseases based on pattern recognition. Since genotype determines phenotype, abnormal phenotypic patterns are surrogates of diseases. Pathologists are experts in recognizing abnormal patterns and thus diagnose diseases. Besides the morphologic patterns, includ-
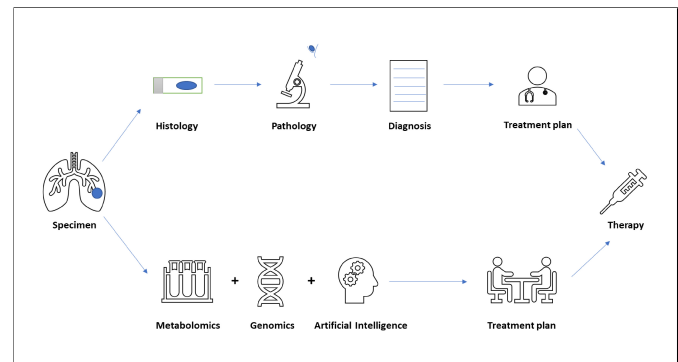

Figure 1: Traditional modern medicine (upper) versus precision medicine (lower).

ing cytological features, architectural changes, reactive backgrounds, and exotic visitors to the organs and tissues, they also evaluate cell types involved in the pathological process by examining markers expressed by the relevant cells, pattern of expression (membranous, cytoplasmic, nuclear, Golgi), intensity of expression (strong, medium, weak), and expression aberrancy (such as CD5 on B cells or CD19 on myeloids). Genetic abnormalities are an important indication of malignancy and certain genetic patterns have been associated with certain diseases, sometimes making genetic abnormality as the only evidence for confirming a disease (such as in myelodysplastic syndrome). Once a final diagnosis has been made, how to manage the patient will be the job of the clinicians and the pathologists will be largely "off the hook".

In contrast, traditional diagnosis will be less important in precision medicine since the diagnosis, surrogate of the disease, will be replaced by molecular data on genomics, proteomics, metabolomics, and transcriptomics, etc. and pathologists will provide therapeutic strategies directly to the clinicians (Figure 1). For example, if Disease A occurs in patient X it might be managed differently from a similar disease (Disease A') in patient Y because patient X is different from patient Y. You may argue that penicillin is effective against streptococcal infection in both patient X and patient Y. Not necessary! Did
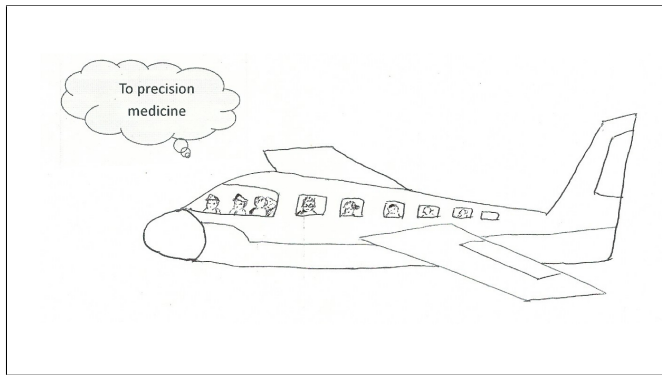
Figure 2: Healthcare team on way to the precision medicine. Pathologist, radiologist and omicsist are in the cockpit; whereas the clinicians are in the passenger seats.

you consider history of allergy in patient X and no allergy in patient Y and their possible drug resistance before you prescribe penicillin? Yes, you did, but because of the prevalence of drug resistance, physicians almost always prescribe Augmentin to patients with recurrent streptococcal infection. We are currently using cytotoxic drugs (R-CHOP) to treat diffuse large B-cell lymphoma (DLBCL) based on our experience with worldwide clinical trials, but since using this therapeutic regimen is not considering the differences in cytotoxicity and metabolism of the drugs in each individual patient, there is only a 50% cure rate [6] and a 60-70% 5-year survival rate [7]. With precision pathology specific therapeutic targets will be identified for DLBCL of each patient whose genetic makeup and metabolism will be well understood. Therapeutic strategies will be tailored to each patient with a regimen and dosage even though all the patients are inflicted with the same DLBCL. This is the beauty of precision medicine.

Instead of looking for morphologic features, cell types, architectural changes, and/or genetic abnormalities like those of the past documented diseases, the precision pathologist will search for the therapeutic targets that are deemed responsive to the available drugs. The precision pathologist will also examine the unique pharmacogenomics and phar-

macometabolomics of the patient. Based on the therapeutic targets of the disease and the pharmacogenomics and pharmacometabolomics of the patient, the precision pathologist will design a therapeutic strategy with the clinicians who clinically manage the patient. The pathologist has never been so involved before in managing patient and this is the major role change for pathologist in precision medicine.

Driver versus Passenger in Patient Care Plane

Pathologists are typically consultants to clinicians and passively providing advices and suggestions to the clinicians who directly take care of the patients. This situation will change in the future precision medicine. According to one vision, healthcare system is like an airplane [8], and within the patient care team pathologist will be the pilot with radiologist being the co-pilot and expert on "omics" as the flight engineer (Figure 2). With information provided by the "omics" expert, the pathologist will guide the treatment plans and the radiologist will identify the accurate location of lesions. Although it remains controversial whether this metaphor is accurate, this vision stresses the important role of pathologist in the future precision medicine.

Acknowledgements

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