Review

The Role of Pathology in Precision Medicine

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Abstract: In the era of precision medicine, complex disease-specific and host-specific metrics are becoming essential and must be implemented in patients care. Because of cancer heterogeneity, precision medicine is more impactful in oncology than any other field. However, it is becoming increasingly difficult to keep up with the vast knowledge and fast pace of advances in cancer management and therapy. For that current cancer care requires multidisciplinary team approach. Pathologists are very important component of this team and their role is expanding significantly. Pathologists must not only provide the morphologic diagnosis, but they are required to provide information on the biological and molecular characteristics of the disease and the host. They must present and discuss the clinical relevance of the various molecular and biological findings in selecting therapy, predicting prognosis and planning the course of management. This article discusses the changing role of pathologists in the era of precision medicine and the importance of more engagement of pathologists in the daily clinical decisions and patient care.

Keywords: Precision Medicine, Pathologist, Genomic, Diagnosis, Clinical Trials

Introduction

Precision medicine requires precision pathology [1]. While companion testing is one part of precision pathology delivering information on a specific biomarker, pathologists are also required to deliver a precise diagnosis, define the underlying biological and molecular abnormalities, define the potential clinical course and prognosis, and point out the targetable abnormalities for therapy selection. Furthermore, pathologists can play a major role in monitoring the efficacy of therapy, determining response, and predicting relapse.

The old concept of the pathologist as the physician who looks through the microscope and makes diagnosis is no longer acceptable. Pathologists must be involved in all aspects of patient's care, and pathologists' role is becoming more difficult and more demanding. A modern pathologist must be a scientist, diagnostician, and, to some degree, a clinician. Furthermore, pathologists must have proper familiarity with the financial implications of reimbursement on the clinical decisions. This broadening role of pathologists represents a significant challenge for pathology practices and departments as well as hospitals. These challenges must be addressed in the training programs and the workflow in pathology departments.

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New drugs and therapeutic approaches are being developed at a faster pace than ever before and this is helping in changing the practice of medicine. The state of the science behind the practice of medicine is very exciting in this fast paced expansion in our knowledge of diseases. Moreover, a tremendous array of tools and technology are now available for pathologists to use and explore in daily practice. Keeping up with all these changes requires hard work and continuous focus on education and learning. Pathologists must take the lead in adapting and implementing the new changes. This article is an attempt to define the changes in the practice of pathology, to define the challenges in our practice, and propose some ideas to address them.

Precision Medicine and Precision Pathology

The promise of precision medicine is to provide medical care that is individualized for the specific disease for the specific patient [2]. While pathologists were the first to point out the variation between patients in qualifiable fashion, now it is also important to quantify this variation. For example, pathologists have pointed out for many years that not all adenocarcinomas of the colon are the same; now it is important to point out the specific differences, like the presence or absence of mutations in *KRAS*, *BRAF*, *APC*, or others [3]. Furthermore, it is becoming important to designate differences in the host constitution and corresponding response to their disease. A patient with a germline specific polymorphism or mutation may require a specific treatment, as outcome might be different from those patients without this specific germline abnormality [4]. Additionally, the host immune response to the disease might be different between patients. For example, solid tumors with lymphoid cells infiltrating the tumor may dictate an outcome that is different from that in patients with a less active tumor microenvironment [5].

The pathologist's evaluation of the disease must consider and report all these variations and must explain their clinical implications. This is particularly relevant in cancer diagnosis and treatment, but can be expanded to other non-neoplastic diseases.

Pathologist as a Member of Multidisciplinary Team

Precision medicine requires a precise understanding of the patient's status and the exact features of the disease. This requires multidisciplinary team including: internist, oncologist, pathologist, pharmacist, radiologist, and frequently, radiotherapist and surgeon. The interaction between various members of the team is very important for the delivery of proper therapy carefully tailored for the specific patient. Pathologists' workflow and pathology departments must be structured to accommodate such interaction.

Pathologists as the Keepers of Tissue Samples and Biological Samples Repository

Samples are extremely important in the age of biomarkers. Pathologists should be responsible for determining what type of samples need to be collected, as well as dictating their quantity and quality. Furthermore, they should be very careful in using these samples. They should pay careful attention to all needed tests and how tissue can accommodate all needed tests, not only at that moment but also potentially in the future. This is particularly important since frequently core or needle biopsy is used to obtain samples. Residual samples should be carefully logged, categorized, and stored. Pathologists should be responsible for maintaining and updating a database that clearly characterizes the samples, provides protocols and tools for de-identification. The database must be easily searchable and should be updated for any change in inventory. This should

not only be limited to tissue samples collected for the purpose of establishing diagnosis, but also include samples collected proactively for potential future research and innovation. Samples should be collected with flexibility and an open mind to allow for future development helpful to individual patients, to pure research, and to the development of new assays. For example plasma, serum, urine, and even saliva might be appropriate samples for certain tests. Pathologists should be familiar and responsible for the proper process for protecting patients' rights and confidentiality and making sure that proper consent and Institutional Review Board approval are obtained.

Pathologists and Tumor Heterogeneity

With targeted therapy, it is important to distinguish between founding or trunk mutation and progressor or secondary mutations. Targeted therapy when used to eliminate cancer should target the founding mutation. Heterogeneity within the tumor sample and the co-presence of multiple subclones in a tumor should be noted by the pathologist using various technologies including morphology, immunohistochemistry, and molecular sequencing. It is very imperative that this heterogeneity is studied fully, described and explained to the treating physician, so therapy decisions are tailored to target all subclones.

Pathologists and Clinical Trials

Pathologists are frequently asked to be involved in clinical trials not only to confirm diagnosis and evaluate response, but also to design and test biomarkers that can be used for selecting patients or for correlative exploratory research. The pathologist must be engaged in the entire process and should give full advice on proper testing for confirming diagnosis or response as well as on the practicality and robustness of the methodology employed in the test. Selecting the proper technology to be used in the companion testing may make a huge difference in determining the robustness and the accuracy of the companion test, and as such, the pathologist should guide development of companion testing with a practical scientific approach and consideration of potential commercial issues or problems that may arise.

The focus of pharmaceutical companies is usually to get approval for a drug and a consulted pathologist must balance the interest of the pharmaceutical company and selection of the proper companion test that is reliable, cost-effective, and can be easily adapted in various laboratories.

Pathology Reports

Due to an exponential expansion of knowledge in biology and medicine, pathology reports should not only be comprehensive, but also provide basic and practical information on the findings, as well as recommendations for therapeutic approaches. Pathology reports should provide a general discussion of the clinical relevance and implications of the morphologic, immunophenotypic, and genomic findings. This information will help the treating physician to make more educated decisions about the patient and course of action.

Keeping up with scientific developments and individual patient data and having it available to pathologists frequently requires help from databases and algorithms that should be developed by pathology practices as dictated by specialization. Pathologists should take advantage of artificial intelligence and computer-aided decision making in their daily practice.

Furthermore, patients currently have the right to request and read their own pathology reports, and, in my opinion, pathology reports should incorporate a section that describes and summarizes the findings in simple terms for a lay person.

Pathologist and Commercial Diagnostic Companies

With the advent of highly sophisticated technology requiring specialized skill and expensive instruments, diagnostic pathology is becoming more dependent on reference laboratories that have the volume to justify investing in expensive instruments and recruitment of highly specialized and skilled individuals. However, this creates a new challenge for pathologists, both the pathologists referring samples to commercial laboratories and the pathologists recruited to work for those commercial laboratories. While commercial diagnostic companies and hospital-based laboratories are expected to generate profits, pathologists must play a significant role in preserving the integrity of pathology practice and offer the most reliable services for their patients with the concept of "do no harm, medically nor financially".

Selecting and ordering the appropriate medically necessary and cost-effective test in the current medical practice is becoming very difficult and complex. Practicing clinicians need the pathologist's advice in selecting the proper and cost-effective tests and it is the duty of the pathologists to be current and knowledgeable about the various technologies and tests offered on the market. Furthermore, pathologists employed by commercial companies should insist on being the ones who approve clinical tests and must resist the pressure of the business and should not approve or offer tests that are not robust or reliable. Unfortunately, some commercial companies are driven by the market pressure and offer tests that are unreliable or provide tests that are not supported by proper clinical data. On the other hand, some tests provide important information that should be considered in light of other clinical and laboratory findings, but not covered by the Centers for Medicare and Medicaid Services (CMS) or insurance companies and these tests can be very valuable for patient care. Pathologists should order the best and most accurate tests when needed, irrespective of the coverage by insurance companies or CMS. Not all clinical laboratory tests give a binary result and many provide information in gray zones that, when considered with other findings, may give highly important information. For example, patient with a mutation in exon 18 of *EGFR* gene may respond to EGFR-TKI even though most such inhibitors are not clinically tested against mutations in exon 18 [6]. When a pathologist is faced with selecting a test that includes mutations in exon 18 of *EGFR* in addition to standard testing (exons 19, 20 and 21), *vs.* a test that does include exon 18, the pathologist should select the more comprehensive test and should explain the lack of confirmation of response data for mutation in exon 18. Commercial companies may choose the test that is reimbursable, but pathologists should order and approve the most comprehensive and reliable test. Pathologists should not accept offering a test that may deprive the patient from receiving potentially effective therapy.

Most commercial companies evaluate pathologists based on productivity and exert pressure to do more and generate more revenue. While productivity should be the pathologist's goal, it should not compromise patient care. Some cases may require significantly more time than others and each case should be given the proper attention and time to be fully evaluated.

Challenges for Pathologists

Recently, the FDA has announced its interest in regulating laboratory testing and laboratory-developed tests (LDT). While the intension of the FDA is to assure that clinical laboratories are offering safe and reliable testing, considering the rate of advances in the field of testing, the added extra level of complexity needed in going through FDA approval may hamper the rate of progress in testing. Further, by the time a test is approved by the FDA, the technology or the principle of such testing may be obsolete. Pathologists practice medicine when they invent a new test, but they do not manufacture a device. Tests must

take advantage of the state-of-the art technology and the most updated scientific knowledge. Pathologists are trained and should be continuously educated to perform this job and this functionality.

Unfortunately, some tests being offered by commercial companies are not well-developed and these companies may make statements that are not well supported by evidence and such practice is forcing regulatory agencies such FDA to interfere and regulate those tests. Therefore, it is necessary for pathologists to be more vocal and more active in regulating diagnostics and not allow few commercial companies and welling pathologist to compromise the integrity of clinical testing.

Summary

It is a very exciting time to be practicing pathologists. There is more than ever a need for laboratory testing and biomarkers to guide clinicians in their clinical decisions. Diagnoses and diseases classifications are becoming more dependent on solid molecular and immunophenotypic markers and less dependent on subjective morphologic features. Biomarkers are becoming the cornerstone for most of the new therapeutic approaches in precision medicine. However, pathologists must adapt to the rapid changes in medicine, biology, technology, and informatics. They must be deeply involved in the molecular advances and they must lead in integrating the new knowledge and technology into every day medicine. Accepting and implementing of machine learning and artificial intelligence might be necessary to keep up with ever field of medicine and pathology.

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