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REVIEW AND PERSPECTIVES

Personalized cancer medicine and the future of pathology

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Abstract In February 2011, a group of pathologists from different departments in Europe met in Zurich, Switzerland, to discuss opportunities and challenges for pathology in the era of personalized medicine. The major topics of the meeting were assessment of the role of pathology in personalized medicine, its future profile among other biomedical disciplines with an interest in personalized medicine as well as the evolution of companion diagnostics. The relevance of novel technologies for genome analysis in clinical practice was discussed. The participants recognize that there should be more initiatives taken by the pathology community in companion diagnostics and in the emerging field of next-generation sequencing and whole genome analysis. The common view of the participants was that the pathology community has to be mobilized for stronger engagement in the future of personalized medicine. Pathologists should be aware of the challenges and the analytical opportunities of the new technologies. Challenges of clinical trial design as well as insurance and reimbursement questions were addressed. The pathology community has the responsibility to lead medical colleagues into embracing this new area of genomic medicine. Without this effort, the discipline of pathology risks losing its key position in molecular tissue diagnostics.

Keywords Translational research · Next-generation sequencing · Whole genome analysis · Molecular pathology

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Background

In the past, pathologists have defined cancer subtypes based on anatomic origin, clinical behavior, and microscopic morphology. Therapy was based on morphological classification and extent of spread as translated in stage, as well as protein-based tests such as immunohistochemistry. Although immunohistochemistry is still the most frequently used approach for cancer subtyping beyond morphology, the past 10 years have brought a revolution in the understanding of the molecular pathology of cancer [1]. We are increasingly aware of its enormous complexity, mainly due to the emerging technologies to characterize cancer and to derive its molecular characteristics, which are increasingly relevant in the practice of oncology. Molecular technologies, such as the identification of characteristic translocations in leukemias and lymphomas and categorization of tumor types based on expression profiling, had changed our understanding of certain cancers [2, 3]. In solid tumors, the identification of erbB2/*HER2* amplification in breast and gastroesophageal cancer led to the development of anti-HER2 therapeutics (trastuzumab, a monoclonal antibody; lapatinib, a small molecule tyrosine kinase inhibitor) that inhibit this protein specifically [4, 5]. Additional examples include *c-kit* and *PDGFRalpha* mutations in gastrointestinal stromal tumors [6], tyrosine kinase mutations of the *EGFR* gene in lung cancer [7, 8], mutations in the *BRAF* gene in melanoma [9], or the *EML-ALK* gene rearrangement in lung cancer [10]; all of which have the potential to render tumors extraordinarily sensitive to specific inhibitors. Certain biomarkers can also indicate when patients will not respond to a specific therapy, e.g., *K-RAS* mutations which render colorectal cancers unresponsive to anti-epidermal growth factor receptor (anti-EGFR) therapy with cetuximab or panitumumab [11, 12]. In recent years, pathologists have contributed profound knowledge to the understanding of these molecular alterations in specific tumor types [13]. In many of these examples, routine clinical practice has changed dramatically. However, the majority of patients have tumors that do not carry these particular genetic changes which therefore do not respond to such treatment. The percentage of patients responding to these new drugs is often below 30%. Therefore, future tasks include profiling these cancers further and to identify additional molecular aberrations that will lead to better therapies. This should be the focus of intensive research projects in pathology.

The goal of personalized cancer medicine is to understand the specific characteristics underlying a particular individual's disease and then match therapy to the molecular characteristics of this case. "The right drug, the right dose, for the right patient, at the right time" is the goal of personalized medicine [1]. The personalized approach has two major problems: complex biology and complex economics [14, 15]. The European Medicines Agency has already approved around 15 drugs for cancer therapy that have been designed to hit a particular molecular target. The pathways involved are often multiple with complex interactions between them which are mostly not well understood [16, 17]. Alterations in various genes, other than the predicted therapeutic target, can also significantly affect the response of a patient to a targeted therapy. As an example, inhibition of the mTOR pathway increases mitogen-activated protein kinase activity [18]. Therefore, the complex network of molecular alterations, signaling pathways, the cellular context, and the response to a particular therapeutic regimen represents a challenge for future approaches in personalized medicine.

The economic dimension is due to the fact that most targeted drugs are extremely expensive. As a result, healthcare systems and insurance companies are confronted with huge problems caused by rising health care expenditures. Targeted drugs need to be accompanied by predictive molecular diagnostic tests to identify suitable patients, yet many healthcare systems have no mechanism to pay for these tests. These companion "one-gene tests" are the domain of molecular pathology. Molecular pathologists have the expertise and the knowledge about many gene mutations identified by molecular tests; they have developed quality standards for testing, and they have developed fellowship training programs in Europe.

The movement towards personalized genomic medicine is currently associated with the development of novel high throughput genomic technologies. These tests reach beyond traditional personalized medicine, enabling the adoption of personalized genomic medicine. Pathologists should be at the forefront of embracing such new technologies [19]. An understanding of modern technologies that profile DNA, RNA, proteins, and metabolites will be essential for pathologists to make personalized medicine a reality [19].

Next-generation genomic sequencing—threat or opportunity?

The human genome sequence was completed more than 10 years ago. Improvements in sequencing technologies led to the "less than 1,000-dollar genome", which is now a reality. At the moment, these new technologies are widely used in research, but they have the potential to revolutionize medical practice. Next-generation sequencing technology may lead to fundamental changes in medical care, where pathologists could provide the necessary knowledge of interpreting genomic information in the context of the disease. However, pathologists have no "birthright" to this technology [19]. Therefore, next-generation sequencing (NGS) may challenge their traditional role. Other medical disciplines and private companies have now their own

interest in these technologies, even as clinical diagnostic tests [20]. Such drivers are further pushing pathologists to demonstrate their expertise in this rapidly evolving area of personalized medicine. One area where a desperate need exists is in the organization and coordination of programs for training in genomic medicine during the pathology residency period. Pathologists should seize the opportunity to take the lead in the translation of these new technologies and to demonstrate their value as routine diagnostic tests.

Pathologists also have to prove that genome-based testing is cost-effective, sufficiently rapid, and can optimize evidence-based precision diagnostics [21, 22]. The pathology community cannot claim ownership of these most recent technological innovations in genome sequencing, but should demonstrate competence in this field. Clinical genetic testing is also performed by various other specialties, e.g., clinical pathology, clinical genetics, oncology, clinical chemistry, microbiology, and pharmacology. With NGS, private, non-hospital-based companies have begun to offer genetic testing that might bypass pathology. Examples include OncotypeDX with their breast cancer assay determining the expression of the 21-gene panel [23] or new start-up companies like Foundation Medicine, offering NGS approaches to cancer genome analyses for personalized medicine. When NGS and whole genome analysis (WGA) can be performed at costs that significantly undercut current charges for single-gene testings, many other institutions outside pathology will offer such clinical tests. It may be that current "one-gene tests" are replaced by NGS testing that will be more powerful and more cost-effective. It is imperative that pathologists take the lead, demonstrating which tests are most powerful and most cost-effective [21, 22, 24]. Only when well-designed clinical studies convincingly demonstrate the predictive value of NGS- or WGA-based tests, will the implementation of such molecular tumor profiling become accepted and integrated in diagnosis and treatment of cancer. Personalized diagnostic technologies will aid in the stratification of patients with specific molecular alterations for a clinical trial. It has been shown in the past that pathologists can significantly contribute to clinical trials, e.g., EORTC trials with colorectal carcinoma patients [25]. These well-designed trials allowed identifying the relevance of k-RAS mutations in colorectal cancer. In the future, clinical trial design will be based on a genotype that can be targeted, rather than the morphological classification. Selection of patients on the basis of the mutations their cancer carries will be challenging, but might be the way to go for types of cancer with specific mutations at lower frequencies. NSCLC patients, for instance, can harbor activating mutations in EGFR, but also k-RAS, BRAF, or translocations involving ALK. Such alterations may be present in less than 2% of patients with prostate, gastric cancer, and melanoma, but these may be sensitive to RAF or MEK inhibitors [26]. The understanding of specific molecular pathways can also help to interpret clinical trial data and enhance our understanding of the biology of response or resistance. Well-designed clinical trials, in combination with novel genomic technologies, will require the involvement of pathologists' expertise, which as a consequence must be involved very early in the design of clinical trials [27].

Above all, when genomic tests of tumors are considered, it is essential that the test be performed on nucleic acid extracts *from tumor cells.* Certainly for solid tumors, only pathologists can make this determination; *genomic analysis in the absence of pathologic assessment risks the generation of meaningless results.*

Pathology today—strengths and weaknesses

Personalized genomic medicine is an issue for the entire field of medicine. The medical community now has the task of integrating this new domain into medical practice [19]. Pathology should take leadership in personalized genomic medicine by partnering with other medical disciplines. Diverse disciplines such as genetics, clinical chemistry, microbiology, immunology, and bioinformatics are engaged in molecular diagnostics. These specialists should work closely together with pathologists. At the moment, pathologists are important members of all tumor boards, where individualized treatment decisions are made. We rely on our clinical colleagues to send us specimens from patients who have sought medical attention for a specific problem; the case is assessed, diagnosed, and interpreted and a report is issued. Pathologists are able to develop a "diagnostic algorithm" with conventional histopathology in combination with immunohistochemistry [28]. This basic evaluation can be supplemented by disease-specific analyses such as other "one-gene tests", and potentially WGA or NGS. Therefore, pathologists are in a pivotal position to include and integrate genomic results with tissue-based morphological assessments to generate a complete report for the treating oncologist and the patient (Fig. 1).

In Europe, pathologists have different strategies to demonstrate competence and expertise in molecular testing. In Germany, a quality assurance initiative has been organized. Interlaboratory tests as part of a quality assurance initiative in pathology (QuIP) are run under the auspices of the German Society of Pathology. Similarly, in Italy and Spain, two quality assurance systems for molecular testing of EGFR and KRAS mutations under the supervision of the National Associations of Oncology (AIOM) and Pathology (SIAPEC) and the Spanish Society of Pathology, respectively, have been validated. The QuIP system sets quality standards for all molecular pathology testings. Similar systems exist in the UK for a number of tissue-based molecular tests, organized by UK-NEQAS, while EMQN and the European Society of Pathology also organize molecular testing

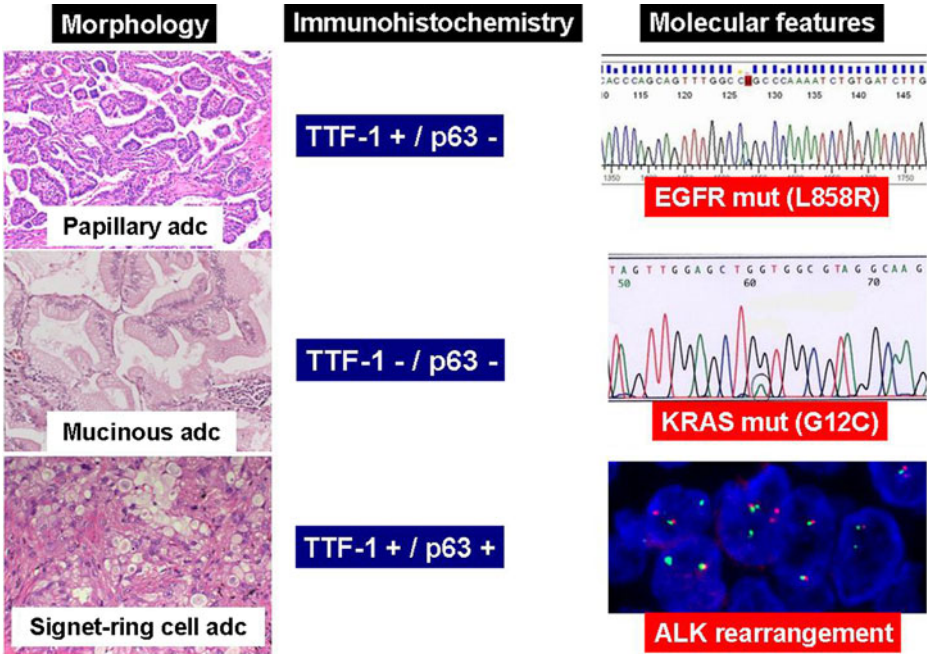

Fig. 1 Integration of conventional histopathology, immunohistochemistry, and disease-specific genetic results in lung cancer

quality assurance programs in various European countries. These systems demonstrate the expertise of pathology to perform such tests and to provide the respective quality assurance programs. National and international recommendations for mutational analysis of EGFR in lung cancer have been also published [29–32].

Given the high cost of targeted therapies and the requirement that these expensive drugs cannot be prescribed without testing, France has found its own solution: In 2005, the country confirmed payment for treatment of every citizen shown to be likely to benefit from targeted drugs. Its National Cancer Institute set up 28 platforms for molecular genetics at those university hospitals and cancer centers with expertise in both molecular and pathological analyses. Biopsy samples of cancer tissues are sent from all over France, to these platforms for a battery of around 20 genetic tests. If in the tissues a molecular signature is identified in any signaling pathway targeted by one of the drugs, the patient gets treated with it. The Czech Republic has a similar system. The French platforms have tested samples from around 50,000 people with lung cancer for alterations in the EGF pathway [14]. Advantages of the centralized system include reduced cost due to large volumes of tests, easier quality control, and free of charge testing for patients. On the other hand, tests are frequently performed outside the primary hospital and tissues have to be sent to an external platform. This can result in a delay of receiving the test results. Given these differences, a European commission's health directorate should help by encouraging European countries to harmonize their health technology assessment by giving recommendations.

Personalized medicine has ethical, legal, and social implications. Privacy issues are a concern for many patients, which must give their consent for treatment. The public has to be educated with regard to the impact of genomic testing. This is a relevant issue for the EU health directory. Furthermore, the requirements for informed consent documents should be harmonized in the European Union. There is a need to protect patients' data, e.g., against discrimination (issues related to health insurance and employment). Patients should not have to fear discrimination. Testing for BRCA1 and BRCA2 genes (implicated in familial breast and ovarian cancer syndromes) were early examples for the contribution of germline features to disease prognosis. Public education on the potential benefits of personalized cancer medicine and individualized treatments are important for its widespread acceptance. When novel next-generation sequencing technologies enter into clinical medicine and become standard of care, public education programs on the ethical, legal, and social implications are needed for patient protection [33].

Conclusions

The meeting participants agreed that there is a need to develop a European strategy to ensure that pathologists are involved in the performance, interpretation, and regulation of omics-based clinical testing, while recognizing the importance of clinical trial-based evidence for performing any particular test. Testing for testing's sake serves no useful purpose. Pathologists have

to develop programs of training and education in genomic medicine, especially in the evolving technologies of NGS and WGA. The European Society of Pathology should assess the current landscape of molecular testing and the reimbursement situation. It should identify barriers and recommend specific actions required to develop a European plan for integration of genomic testing and its interpretation into pathology. It should be shown that if pathologists take the lead in this arena, substantial benefits will be realized, not only for the patient, but also for society at large. The new technologies are very complex. Therefore, the European Society of Pathology should assume leadership when it comes to regulatory challenges for such technologies when performed in pathology laboratories. This includes evaluation of the performance claims of the tests based upon scientific evidence. Tests to be performed in a diagnostic and therapeutic context should be certified after technical validation, notably but not only when it comes to many "in-house-developed tests". The European Society of Pathology should publish standards on assay validation and performance. Consensus recommendations to clinicians and oncologists would also be helpful for personalized medicine, especially in a time with competing test on a commercial market. The European Society of Pathology, through its working group in molecular pathology, should distribute information on clinical trials and issue guidelines on clinical policy in oncology based on the "levels of evidence" approach. Guidelines of the European Society of Pathology would be helpful for different countries to select specific technologies into routine tissue testing.

The future of pathology lies in personalized medicine [19, 34, 35]. Pathologists have the obligation to take a lead in changing both their role, and prevailing attitudes towards that role, away from "just looking into the microscope", towards "integrating the results of both histology and molecular diagnostics" for the benefit of patients. Pathologists must learn to manage the clinical decision-making process by coordinating histological diagnosis and molecular measurements. Pathologists must get prepared to understand their new role, expand their profile, and take new responsibilities.

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