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Editorial

Participation in and support of clinical studies and other scientific investigations – Statement of the German Society for Pathology☆

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ABSTRACT

Clinical studies and preclinical investigations are essential in order to test new therapies and diagnostic techniques aimed at sustainable improvements in the treatment of patients. Fortunately, the number of clinical studies is continuously increasing and pathology and tissue-based research are more frequently involved. Pathologists are essential in this process and committed to support it by joining forces with our clinical partners. The investigative diagnostic technologies we apply to human cell and tissue samples and our specific expertise are essential contributions to the quality and success of preclinical investigations, clinical studies, and the implementation of results into clinical diagnostic pathology. In order to support this process, the German Society of Pathology has formulated a statement on the participation in and support of clinical studies and other scientific investigations with a special focus on tissue-based research.

Background

Surgical pathologists can make a considerable contribution to the quality and success of preclinical investigations, clinical studies and the implementation of results into clinical diagnostic pathology, particularly:

- In the *preclinical phase*, e.g. in the establishment and testing of biomarkers on correspondingly characterized tissue collections, as well as in the development and validation of diagnostic assays.
- During *clinical studies* by testing predictive biomarkers (study-specific tissue diagnostics for study enrollment) and performing supportive tissue-based research.
- In the introduction of new diagnostic methods into clinical routine (roll-out), as well as in the establishment and execution of external, objective quality control procedures and bedside-to-bench research projects that improve the diagnostic application.

Problems

The increasing research activity also brings new challenges for the field of pathology. Pathologists are increasingly asked to make available the patient tissue samples entrusted to them for diagnostic purposes only (=indirect health care) without a primary research/study focus or intention, and in some instances to provide study-related information or perform additional investigations. This opposes pathologists in their role as tissue trustees with a multitude of different unresolved issues, which are exemplified below:

Heterogeneous research landscape

The research landscape is heterogeneous (academic, clinical, industrial etc.) and the aims of the studies and research projects differ. The requests pathologists are confronted with mainly relate to:

- the request of material for histopathological validation for clinical studies (with and without therapeutic relevance) and
- the request of samples to continue research projects or perform additional investigations.

Frequently, background and intentions of these studies are unspecified or unclear on the first contact.

Informed patient consent

In Germany, informed patient consent is required by law and formulated in a study-specific manner (for further information in German, see http://pew.tmf-ev.de/newfile.php). In the case of accessing diagnostic pathology archives the patient is generally not informed that the material is limited and that further use thereof may limit, or even render impossible, subsequent analyzes relevant

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to their health care or other studies (see below). This could cause conflicts in situations where the patient has already consented to participate in other studies or given permission for excess tissue to be used in scientific investigations, for example in the hospital admission contract or a separate informed consent form.

Study-associated tissue collections

In addition to therapeutic goals, some clinical studies aim to create a separate study-associated tissue collection. Upon study completion, these tissue collections may be uncoupled from the project in order to enable further tissue-based scientific investigations. These tissue collections are highly attractive due to their link to standardized clinical data obtained during the course of the study and the well documented treatment background. However, conflicts could arise with the informed consent, if the patients only agreed to investigations occurring as part of the current study. Material originating from a diagnostic pathology archive may not be returned after completion of the initial study and is thus transformed into a research collective and access for further diagnostic or other scientific investigations is reduced or even prohibited. Often, informations regarding the return of the supplied material are lacking; consequently, the generation of a possible separate tissue collective is not transparently addressed.

Proprietorship

A transfer of proprietorship can occur upon supply of material if patient samples from a diagnostic pathology archive are transferred to a study-associated tissue collection and thereafter even to a research biomaterial bank. With the transfer of ownership, indirect diagnostic endeavors can be permanently deprived of the material. There are significant local and international differences regarding the regulations governing transfer of ownership/proprietorship of patient materials.

Study results

The results of tissue analyzes in the context of studies are frequently not conveyed. This is acceptable for clinically irrelevant data obtained in the case of biomarker and licensing studies for new drugs if the results are covered by confidentiality regulations. However, this has to be viewed critically when clinical studies involve an anatomic pathological validation of the primary diagnosis for compliance with the inclusion criteria. In this instance, any differences between primary and study-based pathology results could translate into differences between the information available to the involved parties and lead to conflicts relevant to the patient's past, ongoing, and future medical treatment. The impact of a clinically relevant difference between trial-related findings and preceding clinical diagnostics is frequently not addressed with regard to information procedures, policy for resolution and liability issues, and are rarely implemented by the trial protocols. This is also true for the problem of incidental new findings not only from a liability point of view but also from the perspective of the study participant/patient, whose interests have to be protected. Withholding of clinically relevant incidental findings can damage the trust relationship between patient, clinical research, and the health care systems.

Data protection

As trustee of the diagnostic material (e.g. formalin-fixed and paraffin-embedded tissue specimens, slides, fresh frozen tissue samples), the primary pathologist is responsible for adequate archiving of pathologically relevant, patient-related data and diagnostic material in accordance with the national laws governing data protection. In many clinical studies, the requirements for data protection are violated or cannot be controlled: the pathologist may receive a request relating to a named patient and is asked to provide patient data or a nonpseudonymized assessment and frequently the involvement of personnel not covered by data protection regulations cannot be excluded.

Compensation of expenses

The costs entailed by the workload (selection, validation, and shipment of material, re-archiving of returned samples) are often not considered or defined without consulting involved pathologists. The level of compensation is often not (or no longer) negotiable and may not cover the complementary costs in terms of consumables and personnel. Furthermore, the administration of most institutions deduct flat-rate overhead costs from industrial contributions that are not available to cover specific expenses.

Solving the problems

In order to properly define the problems, a systematic analysis of the current situation in Germany was necessary, aspects of which may probably also apply to other European countries. The analysis also supported the creation of a criteria catalog aimed at four main purposes and target groups:

- The patients, upon whose participation and consent the research in this area depends. By systematic and consequent adherence to a transparent system, trust can be established and patient autonomy is appropriately protected.
- The pathologists receiving a request for material. These pathologists provide, finance, and maintain the diagnostic pathology archive. They are the trustees of the interests of the institute and its governing body, all potentially involved local clinicians and researchers, and the patients. They alone have to be able to decide whether forwarding of material from the diagnostic pathology archive conforms with all relevant regulations and is in the interests of all involved parties.
- Persons responsible for study or project planning and execution, in order to ensure proper conception and performance of a clinical study or a research project.
- The responsible teaching and research institutions (universities, medical colleges) in the protection of their genuine interests.

This statement exclusively considers regional and national aspects and does not relate to international regulations, e.g. American and Asian. The latter would require an in-depth analysis and understanding of various legal systems, which does not fall within the primary purpose of this statement and the central competence of pathologists. However, we hope to strongly encourage international initiatives to ease international studies, as these become increasingly important in modern therapeutic approaches.

Interests and responsibilities

The criteria catalog begins with an evaluation of the interests and responsibilities.

Academic centers

As the predominant institutions interested in maintenance of tissue collections for research and teaching purposes, academic centers (e.g. University Hospitals) have a genuine interest and public mandate to pursue research and teaching activities. Paraffin