



# Confusion—specimen mix-up in dermatopathology and measures to prevent and detect it

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**ABSTRACT** Maintaining patient identity throughout the biopsy pathway is critical for the practice of dermatology and dermatopathology. From the biopsy procedure to the acquisition of the pathology report, a specimen may pass through the hands of more than twenty individuals in several workplaces. The risk of a mix-up is considerable and may account for more serious mistakes than diagnostic errors. To prevent specimen mix-up, work processes should be standardized and automated wherever possible, e.g., by strict order in the operating room and in the laboratory and by adoption of a bar code system to identify specimens and corresponding request forms. Mutual control of clinicians, technicians, histopathologists, and secretaries, both simultaneously and downstream, is essential to detect errors. The most vulnerable steps of the biopsy pathway, namely, labeling of specimens and request forms and accessioning of biopsy specimens in the laboratory, should be carried out by two persons simultaneously. In preceding work steps, clues must be provided that allow a mix-up to be detected later on, such as information about clinical diagnosis, biopsy technique, and biopsy site by the clinician, and a sketch of the specimen by the technician grossing it. Awareness of the danger of specimen mix-up is essential for preventing and detecting it. The awareness can be heightened by documentation of any error in the biopsy pathway. In case of suspicion, a mix-up of specimens from different patients can be confirmed by DNA analysis.

Every year, hundreds of thousands of pages are devoted to diagnostic problems in medicine. In books and medical journals, physicians constantly share their experiences, advance criteria for diagnosis, and alert to diagnostic pitfalls. One tremendous pitfall, however, probably the greatest of them all, is hardly ever mentioned, namely, specimen mix-up.

The true size of that pitfall is unknown. There are only few articles about that subject and most deal with individual

cases. This is not surprising because specimen mix-up would not occur if it could be recognized reliably and studied systematically. In laboratory medicine, analysis in the early 1970s of 5200 control cases smuggled into routine examinations revealed an error rate of 3.5%. The most common of those errors, occurring in 0.89% of all cases, was a specimen mix-up [1]. By contrast, in a survey conducted at hospitals of many countries, the rate of specimen mix-up was estimated

to be about 0.5% [2]. The discrepancy between those data suggests a huge dark figure of cases.

In addition to the dark figure whose true size, naturally, is shrouded in the dark, other factors hamper a systematic analysis of mistakes in the assignment of specimens. Among them are different criteria employed in studies dealing with mistakes in laboratory medicine, some studies including only cases of specimen mix-up that were not recognized and corrected immediately, others many other types of mistakes, ranging from loss of specimens to incomplete labeling of them that could be amended easily [3,4]. Even inappropriate biopsies and incorrect interpretation of reports by clinicians have been dubbed "*laboratory errors*," in accordance with the definition of such errors as "*any defect from ordering tests to reporting results and appropriately interpreting and reacting on these*." [5] Moreover, data from one hospital or laboratory cannot be transferred readily to another, even if the same criteria are employed.

## Methods of quality control

In tests of blood or urine, mix-up of specimens can be recognized in follow-up examinations if one result is not compatible with all the others. In order to facilitate recognition of such mistakes, Nosanchuk and Gottman in 1974 introduced the "delta check" that compares any two consecutive results for a given test on the same patient by subtracting the later result from the prior result and then dividing by the prior result. The delta value is determined for every new test and is compared to previous values. Each parameter has its own tolerance for deviation, and if the latter is exceeded, the respective case is submitted to further investigation [6,7]. Because samples of blood or urine are generally used for analysis of several variables, the sensitivity of the method has been enhanced by introduction of a multivariate delta check [8,9]. Another method advocated to detect laboratory errors is the "split-specimen design," according to which samples from the same patient are analyzed by two different laboratories, and one part is stored away and analyzed only in the case of contradictory results [10]. In addition, co-determination of the blood group with every test, and comparison of it with the known blood group of the patient, has been advocated as a routine measure of quality control, although it does not help to detect mix-up of specimens of patients with the same blood group [11]. Given the rarity of specimen mix-up, the considerable costs and efforts associated with those methods of detection, and the limited sensitivity of them, the value of methods such as the delta check has been called in question [12].

A mix-up of biopsy specimens is even more difficult to recognize than a mix-up of samples of blood or urine, the reason being that results, in general, cannot be compared to

previous or subsequent data on the same parameter. Each biopsy specimen stands for itself. This is not only true for neoplasms excised completely but also for inflammatory dermatoses. Depending on the stage of development of a given lesion, the histopathologic findings in two biopsy specimens of the same disease in the same patient may differ strikingly, and a modification of the histopathologic presentation by unrelated factors, such as irritation, venous hypertension, or another co-existing disease, must always be expected. Even within the same biopsy specimen, histopathologic findings may vary considerably, precluding the "split-specimen design" as a method of quality control. Moreover, splitting a specimen in several portions in order to have them examined by different laboratories, or to keep one portion in storage, would compromise severely the assessment of criteria for histopathologic diagnosis and, therefore, is not feasible for the vast majority of biopsy specimens in dermatopathology. The suspicion of a specimen mix-up is raised especially by divergent diagnoses on the same neoplasm in an incisional biopsy and the subsequent re-excision specimen. However, two different neoplasms in the immediate vicinity of one another are not rare, especially in skin damaged severely by sunlight. Moreover, complete regression of a neoplasm following biopsy of it is a common phenomenon not only in basal-cell carcinoma, but also in squamous-cell carcinomas and melanocytic neoplasms [13-15]. Therefore, failure to find remnants of a biopsy-proven neoplasm, coupled with detection of a different neoplasm, does not necessarily imply a specimen mix-up. It does, however, raise the suspicion of it.

In order to prove or disprove that suspicion, studies can be performed to check the identity of the patient in both specimens. For that purpose, various methods have been proposed, ranging from immunohistochemical determination of the blood group or of the HLA class 1 antigen profile to molecular studies [16-18]. Immunohistochemical methods have advantages in complex cases. For example, in case of suspicion that some of many fragments of tissue in the same paraffin block come from a different patient, molecular analysis may be difficult, whereas differences in the immunohistochemical staining pattern of those fragments of tissue are detectable easily. However, identical blood groups are common, and even when studying the polymorphous HLA class 1 complex with a panel of five antibodies, identical results of different patients must be expected in 1% of cases [17]. Molecular identity testing is far more sensitive. It is performed by short tandem repeat analysis, i.e., analysis of repeating sequences of 2-6 base pairs of DNA also known as "microsatellites." Because the latter show great variation in regard to the number of repeats and often many alleles at a microsatellite locus, they have been chosen for genetic fingerprinting in forensic medicine. With the use of commercially available kits for combined analysis of several loci, the probability of the

same result in unrelated individuals is about 1 to 1 billion. Since the late 1990s, short tandem repeat analysis has been employed increasingly for proving a mix-up of specimens in surgical pathology [18-22].

A mix-up of specimens from the same patient, however, cannot be detected by any of those methods. Moreover, considering the rarity of specimen mix-ups, identity testing is far too laborious and costly to be performed as a routine measure. It is reserved for clarifying the suspicion of specimen mix-up, and the latter arises only if the result of an examination is not plausible. Sometimes, a mix-up of specimens is obvious. For example, if a biopsy specimen from the buttock of a newborn under the clinical diagnosis of a strawberry hemangioma shows a solar keratosis and large sebaceous glands in severely sun-damaged skin, clinical data and histopathologic findings are incompatible. If the next specimen comes in as a solar keratosis from the nose but shows a hemangioma, the issue is resolved. Usually, the question whether the mix-up occurred in the operating room or the laboratory cannot be decided, but all one needs to do for restoring order is to switch the numbers of both specimens.

In general, however, it is not that easy. For example, if there is also a vascular neoplasm in the first biopsy specimen, the histopathologist must be extremely alert in order to identify the specimen mix-up on the basis of anatomical differences or presence or absence of solar elastosis. If the first patient is not a newborn but an adult, this becomes more difficult. It is even more difficult if findings in only a single specimen do not fit, whereas histopathologic findings in preceding and subsequent specimens and in all specimens submitted by the same physician on the same day are compatible with the respective clinical data. There is no chance at all to discover a specimen mix-up if clinical diagnoses and anatomy are similar, e.g., a melanocytic nevus from the chest and a melanoma from the shoulder. In such instances, the mix-up either goes unnoticed or manifests itself months or years later by a local recurrence of the melanoma at the site of the alleged nevus.

The consequences may be dramatic, and they have been described in many case reports in the forensic medical literature. For example, in an elderly patient two biopsies were taken from the colon, one of which was reported as carcinoma and the other as normal bowel mucosa. Because the precise biopsy site had not been specified on the request slip, a subtotal colectomy was performed on the wrong segment of colon. When histopathologic examination of it failed to reveal signs of malignancy, the mistake was clarified by another biopsy of the carcinoma that had been left untreated [23]. Biopsy of a gastric ulcer in a middle-aged woman revealed a carcinoma and resulted in gastrectomy. No residual malignancy was found in the surgical specimen. In an elderly man, a biopsy from the stomach was performed on the same day under the clinical diagnosis of carcinoma. It revealed only a mild gastri-

tis that was treated conservatively. One year later, the patient died from metastasizing gastric cancer. A molecular analysis revealed that the biopsy specimens of both patients had been mixed-up [19]. A middle-aged woman underwent a breast biopsy that was diagnosed as infiltrating carcinoma. Based on this result, a total mastectomy and axillary lymph node dissection was performed. When histopathologic study of the specimens revealed no residual tumor, the original biopsy specimen was re-examined and failed to reveal carcinoma as well. The carcinoma was found in the preceding slide that the pathologist had taken inadvertently twice from tray, the second time giving the diagnosis of mammary carcinoma on the wrong patient [23].

A nostrum to prevent such catastrophes does not exist. Methods of quality control in laboratory medicine, such as the delta check and the "split-specimen design," cannot be applied. In order to prevent a mix-up of biopsy specimens, it has been proposed to ink all incoming specimens with six different colors in a defined sequence and to write down that color on the request form. In a study of 1000 breast core needle specimens, two mix-ups could be detected by a deviation of the color noted on the request form from the actual color of the specimen seen under the microscope. One of those mix-ups was caused by confusion of two paraffin blocks, the other by an incorrectly labeled specimen slide. In yet another case, a mix-up was faked by an incorrect declaration of the color on the request form; in that instance the additional measure caused confusion, rather than preventing it [24]. More importantly, the sensitivity of the method is low because a deviation of colors may be overlooked, a mix-up of specimens inked with the same color cannot be recognized, and a mix-up of specimens before or after procession of it in the laboratory cannot be detected. Most mix-ups, however, occur before procession of the specimen [3,4]. Despite the high effort associated with it, that method does not provide great benefits.

## Standardization

The best way to prevent and detect the mix-up of specimens seems to be good organization of all steps connected with a biopsy, from the surgical procedure itself to labeling of sample bottles and request forms in the operating room, accessioning of specimens in the laboratory, procession of specimens, assessment of histopathologic findings at the microscope, typing of dictations, transmission of reports, and, finally, assignment of reports to the respective patients in the medical practice or clinic. During that procedure, the specimen may pass through the hands of more than twenty individuals in several workplaces, and none of them can be expected to be focused fully on his or her duty in every minute of every day [25].

One of the most effective means of reducing error in that complex procedure is standardizing processes wherever possible. The reason is that work is usually, and most effectively, performed on the basis of automatic, reflex-type behavior, the so-called “schematic control mode,” rather than controlled conscious thought or processing, the “attentional control mode.” Conscious thought is activated by a seemingly new or novel problem for which no preconceived schema for solution exists; it is slow and effortful. With increasing experience, mental schemas to handle recurrent problems are developed and trained by repetitive behavior in myriad corresponding situations. The “schematic control mode” allows experts to function fast and effortless. Once activated by conscious intention, subsequent actions are relatively automatic and usually reliable. However, if misconceived signals initiate a wrong action, the latter is likely to be carried through without being noticed. Examples are slips in which the wrong automatic action is used, such as putting away a slide that has not been studied, and lapses, the omission of an automatic action, such as skipping a slide in a tray or leaving out a key word in a report (e.g., “malignancy” instead of “no malignancy”). Any breach in routine standardized processes carries an enhanced risk of inducing slips and lapses. The latter are far more common than mistakes resulting from failures in conscious judgment and are less likely to be noted because they involve situations perceived as being non-problematic. In order to prevent signals that induce misguided automatic actions, standardization is crucial. In the operating room, sample bottles containing only formalin should always be taken from the same place, and sample bottles with specimens should be deposited at another place and always in the same way. In the laboratory, sample bottles, tissue cassettes, paraffin blocks, and slides should always be arranged in the same manner, the intent being to make it difficult for individuals to err by allowing them to function reliably without conscious thought [26,27].

## Computer-assisted work

Another means to prevent mistakes is automation of processes. For example, when labeling tissue blocks by hand, the same number may accidentally be accorded twice, digits may be interchanged, or they may not be written clearly and may be misread later on. Automatic labeling of blocks or specimen slides in a printer prevents such mistakes (Figure 1) [4,20]. The incorrect transcription of data, such as name or date of birth of the patient or number of the biopsy specimen, can be prevented by bar codes. Once those data have been converted into a bar code, they do not need to be typed anew in subsequent work steps. In laboratory medicine, a dramatic decrease of specimen labeling mistakes has been reported from numer-



**Figure 1.** Slides with handwritten and printed pathology numbers. Even with clear handwriting, characters do not look exactly the same. For example, the lower horizontal bar of the number 2 on the middle slide is rather short; as a consequence, the number might be read erroneously as 7. Among thousands of slides, there are always some handwritten characters that may be misread. Printed numbers prevent such errors. [Copyright: ©2014 Weyers.]

ous medical centers following adoption of a continuous bar code system [28]. In laboratories receiving specimens from external institutes, a continuous bar code system is difficult to implement, but bar codes should at least be used within the laboratory. In one study from a pathology department, adoption of a bar code system led to a reduction of specimen labeling mistakes by 98% [4]. Ideally, bar codes should be used not only for labeling sample bottles and request forms but also for tissue cassettes, paraffin blocks, and slides, but the costs for establishing such a system may be prohibitive. Moreover, it must be kept in mind that one-dimensional bar codes are not perfectly safe but may occasionally be misread. Therefore, correct scanning should be confirmed by checking the patient’s name on the request slip.

Computer-based working processes have the advantage of a clear typeface. Obviously, toners of printers should be replaced in time, as weak printing may lead to reading or scanning errors. With handwritten data reading errors are far more common. Unfortunately, little value is attached to legible writing. Any information that cannot be deciphered by downstream persons, not all of whom possess broad medical knowledge, is worthless.

Though readability is a great advantage of computer-based processes, it is not the most important one. Without the facility to transfer a brief constellation of letters or numerals at the push of a button into an elaborate text, medical care in its modern form would be unthinkable. However, the tremendous easement provided by computers goes along with risks. A text typed or written traditionally may be replete with typing errors, but as a rule a word remains intelligible even in the case of incorrect typing. By contrast, the accidental



**Figure 2.** Entry of data from the request form in the computer. (A) Correct: request forms lie on top of one another so that only the uppermost one is visible. After completion of the entry, the uppermost form is turned over and is placed back-side-up on the pile of finished forms on the left. (B) False: Request forms of several specimens are scattered across the desk. In case of a distraction, e.g., through a telephone call, the risk is considerable that data from an unrelated request form will be entered when resuming work. [Copyright: ©2014 Weyers.]

transposition of letter characters or numerals in a computer code may create a completely different content, especially if that code is very brief. Therefore, the striving for simplicity and brevity should not be exaggerated; a certain measure of redundancy is essential. A negative example in that regard are computer codes like “7A” or “10B” that have been used for decades at the world’s leading laboratory of dermatopathology by A. Bernard Ackerman in New York City. Those brief codes are error-prone because a slip of the tongue or a minimal deviation of one finger on the computer keyboard suffice to turn a “7A” into an “8A,” thus creating a different diagnosis. By using codes that are slightly longer and reflect their content visibly, such as “Pso-vulg” for psoriasis vulgaris or “Gran-an” for granuloma annulare, those sources of error are mitigated. Even with such codes, however, sources of error must be kept in mind. If two codes resemble one another in their visual presentation or phonetically, such as “Gran-an” and “Gran-ang,” the diagnosis of richly vascularized granulation tissue may be given for a case of granuloma annulare. Recognition and elimination of such sources of confusion enhances the reliability of histopathologic diagnosis.

Redundancy also implies that at least two unrelated data should be provided side by side at each work step, such as the name of the patient and the date of birth or a unique patient identifier on all sample bottles and request slips. Labeling bottles with the name only has been found to increase the rate of mistakes in specimen identification [29]. If the names of two patients are similar, as in married couples, siblings, or parents and their children, a special warning sign may be helpful, e.g., color marking of the forename. In the laboratory, the pathology number should be accompanied by the patient’s name. This is not always possible. For example, tissue blocks are too small to carry several data. In the absence of control by the patient’s name, diligence should be heightened, e.g.,

by double-check of the correct sequence of tissue blocks and by reading out pathology numbers in a low voice at the beginning of each new procedure. When pathology numbers are typed or scanned by histopathologists or secretaries, the name of the patient should always be controlled and either dictated or read in a low voice before dictating or typing the code of the diagnosis.

The computer system should not allow two files of patients to be opened at the same time so that the accidental entry of data into the wrong file becomes impossible. A particularly helpful, but also risky, option provided by computers is the “copy and paste” function that allows an elaborate text to be copied into a different file. Texts that have been marked are kept in the computer’s clipboard, and if the “paste” function is activated accidentally later on, the copied report may be issued for an unrelated biopsy specimen unless the clipboard has been cleared previously.

## Order

An essential requirement for every step in the biopsy pathway is order. The aura of a “creative chaos” cherished by some pathologists and created deliberately by piling up trays with innumerable slides in all corners of their room, intermingled with memos, medical journals, and used coffee cups, is dangerous. Workplaces must be tidy, no matter whether in the operating room or at the computer, laboratory bench, or microscope. One of the chief rules is to keep only one procedure in sight. When typing down the data of patients or dictating or typewriting histopathology reports, requests slips may lie on top of one another so that only the uppermost one is visible, but never side-by-side (Figure 2A, B).

In the operating room, the file of the current patient should be separated from all other files. Sample bottles should





**Figure 3.** In a patient in whom five biopsies were performed, specimens 3 and 4 cannot be distinguished from one another because Roman numerals were used for labeling sample bottles. The Roman numeral 4 cannot be recognized clearly. [Copyright: ©2014 Weyers.]



**Figure 4.** Because the top of one of those sample bottles was not closed tightly, formalin leaked out. The bottles were labeled with a permanent marker pen that was dissolved by formalin. As a consequence, the specimens in the sample bottles cannot be correlated reliably with the biopsy sites noted on the request forms. [Copyright: ©2014 Weyers.]

be labeled and request forms completed immediately after the procedure and should be removed for postage before the next patient is called in. If this is not done, and several files with adhesive labels carrying different names are deposited on the same desk, or unmarked bottles with biopsy specimens of different patients are kept in the same room, there is a great risk of confusion. Confusion may also be caused by labeling bottles and request forms prior to the biopsy because the course of action is often changed during the procedure, e.g., by performing an additional biopsy, by abstaining from a biopsy, or by changing the sequence of biopsies [20]. In such instances, empty bottles or request forms for biopsies that have not been performed are being posted, or the numbers or declarations of the biopsy site on bottles and request slips do not conform to one another.



**Figure 5.** The adhesive labels used to mark those sample bottles did not adhere but became detached. As a result, sample bottles cannot be distinguished from one another. The only option to dissolve this dilemma is correlation of histopathologic findings with the diagnoses and biopsy sites noted on the request forms. If biopsy sites and diagnoses are similar, however, correlation of biopsy specimens and request forms becomes a guessing game. [Copyright: ©2014 Weyers.]

If several biopsies are performed on the same patient, the bottles containing specimens should be put away in a defined, unchangeable sequence before labeling bottles and completing request forms after the procedure. Numbered compartments into which bottles are being placed help to prevent confusion of them. When numbering consecutive bottles, Arabic numerals are preferable to Roman ones because the latter are prone to confusion. For example, the Roman numeral “III” may be read as “II” if two bars are placed too close to one another, or as “IV” if one of the bars is written slightly obliquely (Figure 3). Before removing bottles for postage, it should be checked that all bottles contain a specimen, that they are labeled correctly with all requisite data, and that the covers are screwed down tightly. If covers are loose, and formalin leaks out, it may render labels illegible. This is the case especially if bottles are labeled with a permanent marker pen. The ink of marker pens is dissolved by formalin (Figure 4). Use of adhesive labels with written or printed data is preferable. Depending on the batch, however, not all adhesive labels adhere firmly. Therefore, firm adherence of them should be checked (Figure 5). In addition, sample bottles and request forms should be checked for completeness and concordance in regard to names, numbers, and biopsy sites. Bottles should then be placed in a closed plastic bag before being sent off in one envelope together with the corresponding request forms. According to a current survey among American dermatologists concerning medical error in dermatology practice, nine of ten assessment errors involved the biopsy pathway, and the most common of those errors accounting for 18% of them was incorrect information on the sample bottle or the request form [25].

Those data are in accordance with the experience in general pathology. Most errors in the assignment of specimens, according to the literature nearly three quarters, occur in the pre-analytic phase, i.e., in the practice of the submitting clinician or in the laboratory during unpacking of envelopes, correlation of sample bottles and request forms, and numbering of specimens [4,29,30]. Especially in those phases, strict order is essential. The workspace for unpacking envelopes must be big enough to allow sample bottles and request forms from one envelope to be arranged in a clear fashion. Sample bottles should be placed on top of the corresponding request forms. Several specimens from the same patient should be compiled before labeling them with ascending pathology numbers corresponding to the sequence of biopsies indicated on bottles and request forms (Figure 6). Only one envelope should be unpacked at a time; all specimens of that envelope should be numbered and passed on for trimming before the next envelope is opened. Any distraction during that vulnerable phase is associated with an enhanced risk of confusion. Among such influences are missing, incomplete, illegible, or incorrect data on sample bottles or request forms that require consultation of the submitting practice. If specimens must be put on hold for those or other reasons, they should be removed from the work space before the next envelope is unpacked. There should be a separate space for such specimens and the corresponding request forms, if possible with compartments reflecting the reasons for postponement, such as consultation of the submitting practice, decalcification, or longer fixation time for large biopsy specimens.

The order created during unpacking and numerical labeling of specimens must be maintained in all subsequent work steps, including entry of personal data of patients and clinical data in the computer, trimming of specimens using a scalpel to enable them to fit into appropriately labeled tissue cassettes, orderly alignment of tissue cassettes following procession of them in the tissue processor and before embedding specimens in paraffin blocks, orderly alignment of paraffin blocks on a refrigerated plate before cutting sections, cutting sections at the microtome, microscopy of slides holding sections of tissue, and typewriting of reports (Figures 7-10). Any deviation from the ascending sequence of pathology numbers, e.g., by commutation of two request forms in a pile or two slides on a tray, carries the risk of not being noticed and of leading to an error with potentially serious consequences. If there is an interruption in the ascending sequence of pathology numbers, e.g., if one slide has been broken and must be cut anew, the breach should be marked by a placeholder. Other deviations from the rule should also be marked visibly, e.g., existence of several slides for a single specimen. Clear marking of deviations reduces the risk that the histopathologist takes the wrong slide from the tray. If such mistakes happen, they are usually noticed and corrected readily. However, if associated



**Figure 6.** Correlation of sample bottles and request forms in the laboratory. The envelopes contain sample bottles and request forms of several patients. A large workspace for laying out request forms and sample bottles helps to prevent confusion of them. Sample bottles are placed on top of the corresponding request forms. Subsequently, bottles and request forms are marked with adhesive labels containing the pathology number and a corresponding bar code. The correlation of specimens with request forms and the numbering of them should be carried out by two persons who can control one another mutually. [Copyright: ©2014 Weyers.]



**Figure 7.** Once sample bottles and request forms have been numbered, they are arranged in a row, corresponding to a row of tissue cassettes carrying the same numbers. Specimens are then dissected and put into tissue cassettes. The pathology numbers on sample bottles and tissue cassettes must be checked for concordance before taking out and dissecting the specimen. [Copyright: ©2014 Weyers.]

with some other adverse influence, such as an interruption through a telephone call, the risk is considerable that the error will not be discovered when resuming work.

## Cleanliness

In addition to order, cleanliness is an essential requirement in all steps of the biopsy pathway. This is especially true for the operating room and the laboratory bench. Specimens





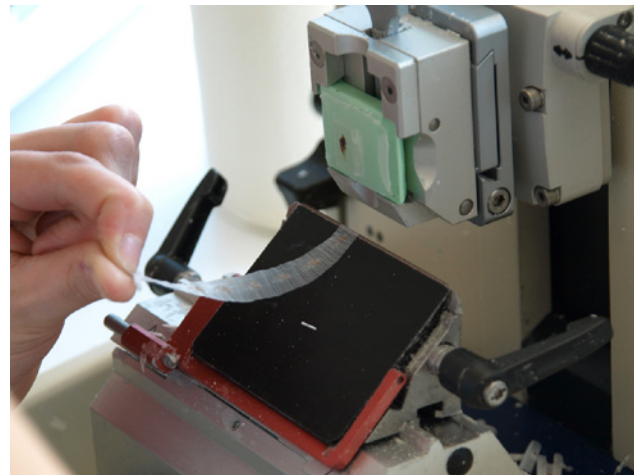
**Figure 8.** Following dissection of specimens, many tissue cassettes with biopsy specimens of different patients are put in a basket and are processed in a tissue processor in order to dehydrate them and to prepare them for paraffin embedding. [Copyright: ©2014 Weyers.]



**Figure 10.** Before cutting sections at the microtome, blocks are cooled on a refrigerated plate. They are arranged in a row according to ascending pathology numbers and corresponding to a row of slides at the other side of the microtome. [Copyright: ©2014 Weyers.]



**Figure 9.** Following procession of tissue, tissue cassettes are taken out of the tissue processor and are once again arranged in a row according to ascending pathology numbers. Paraffin blocks are arranged in the same fashion. The pathology numbers on tissue cassettes and blocks must be checked for concordance before opening the next cassette. Only one cassette should be opened at a time. Pincers must be cleared before taking out the next specimen in order to prevent transmission of fragments of tissue into a wrong block. [Copyright: ©2014 Weyers.]



**Figure 11.** Before clinching the next paraffin block to the microtome, the pathology number on the block and the slide must be checked for concordance and the blade of the microtome cleared from remnants of paraffin or tissue. By moving the block up and down across the blade, serial sections are cut that are connected by paraffin, resulting in thin ribbons of tissue. [Copyright: ©2014 Weyers.]

sometimes fall down during handling of them. Moreover, hard pieces of tissue may flip away when dissecting specimens with a scalpel and, in that instance, one may have to search for them on the floor. For that reason, the floor should be kept very clean, and there should be neither fluff nor other pieces of tissue lying around. Because small pieces of tissue are difficult to see, the floor of a laboratory should be of a light uniform color without any fanciful decor. Cupboards should go down to the floor without leaving narrow empty spaces beneath them that are difficult to clean and to inspect. Specimens of tissue are moist and, therefore, they tend to adhere to instruments. When removing several lesions from

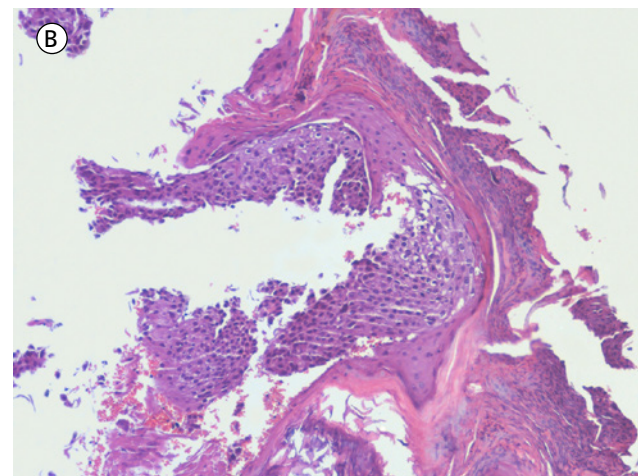
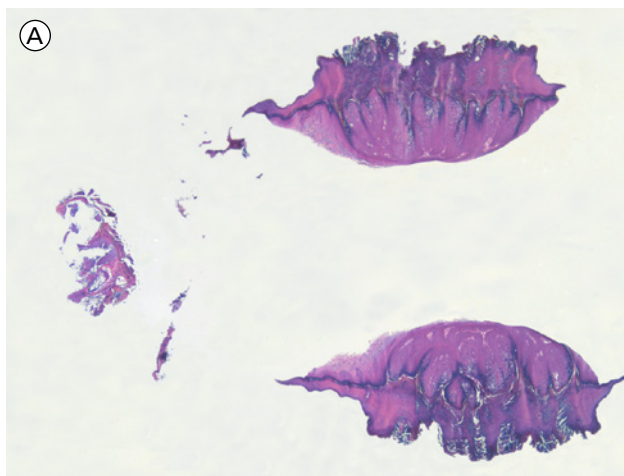
the same patient, fragments of tissue of one lesion may be transferred easily to a wrong sample bottle if abrasors or pincers are not cleared after use. The same may happen in the laboratory when trimming specimens in order to place them into tissue cassettes or when embedding them in paraffin. Subsequently, sections are cut from paraffin blocks at the microtome. Because sections may adhere to the blade, the latter must be cleaned and changed at regular intervals. The tissue is cut in serial sections that usually have a thickness of 5  $\mu\text{m}$  and are connected by paraffin, resulting in thin ribbons of tissue (Figure 11). Those ribbons are transferred to a warm water bath where they are allowed to float on the surface before being scooped up onto a slide placed under the water level (Figure 12). If some sections become detached from the ribbon and are not scooped up, they remain on





**Figure 12.** Ribbons of tissue are transferred to a warm water bath where they are allowed to float on the surface before being scooped up onto a slide placed under the water level. If fragments of tissue become detached, they remain on the surface of the water bath and may be transferred onto another slide. In order to prevent such “floaters,” the water must be kept clean and must be changed at regular intervals. [Copyright: ©2014 Weyers.]

the surface of the water bath and may be transferred onto another slide. In order to prevent such so-called “floaters,” the water bath must be kept clean, and the water must be changed at regular intervals (Figure 13A, B). Contamination of one specimen with fragments of another is one of the most common causes of misdiagnosis secondary to mix-up of tissue [16]. In one study, 0.6% to 2.9% of all slides were found to be contaminated by extraneous tissue. In most of those cases, contaminants were confined to single sections and, therefore, resulted from contamination after embedding of specimens in paraffin blocks [31].



**Figure 13.** (A) Biopsy from the chin of a 34-year-old patient showing typical signs of a verruca vulgaris, namely, acanthosis with elongated rete ridges bent toward the center of the lesion, papillomatosis, hypergranulosis with koilocytes, and compact orthokeratosis with narrow columns of parakeratosis above elongated papillae. In addition to two sections of the wart, there is another piece of tissue on the left. (B) The section of tissue on the left shows crowded nuclei in the lower layers of the epidermis, some hyperchromatic nuclei, loss of the granular layer, and parakeratosis with many nuclei per unit area. These are features of a solar keratosis. The piece of tissue does not belong on this slide but is presumably a “floater” from the water bath. [Copyright: ©2014 Weyers.]

## Mutual control

Because a mix-up of tissue cannot be prevented reliably, internal control is crucial. The latter may be exercised simultaneously or downstream. Simultaneous control means that at least two persons are involved in the same action and can call attention instantly to any error of one another. It is indicated in the most vulnerable steps of the biopsy pathway, including the compilation of sample bottles and request forms in the medical practice before being posted. If bottles and request forms are controlled by two persons with respect to completeness and correct labeling and if that control is verified by countersigning, it will no longer happen that specimens are missing, superfluous, or not assignable when envelopes are unpacked in the laboratory. When compiling material for postage, sample bottles with biopsy specimens from the same patient should not be put in different envelopes.

The accessioning of biopsy specimens in the laboratory, including unpacking of envelopes and sorting and numbering sample bottles and request forms, carries the greatest risk of specimen mix-up. In a study performed at more than 400 institutes of surgical pathology, accessioning accounted for nearly half of all deficiencies in specimen identification [29]. Therefore, it should be carried out by two persons simultaneously. The same is true for the end control of slides, before slides with sections of tissue and the corresponding request forms leave the laboratory and are forwarded for microscopy. The control of the correct, identical sequence of pathology numbers on slides, paraffin blocks, and request forms, and of the concordance of the shape of specimens in paraffin blocks and on slides, by at least two persons is essential (Figure 14). According to one study, the error rate



**Figure 14.** End control of slides in the laboratory. Slides are laid out on trays according to ascending pathology numbers. Before they are forwarded for microscopy, they are checked for the identical ascending sequence of pathology numbers on slides and request forms and for concordance of the shape of specimens in paraffin blocks and on slides. [Copyright: ©2014 Weyers.]

could be reduced from 1% to 0.1% by reading out loud the numbers to another person [20].

Even more important are downstream controls that allow detection and correction of errors of preceding work steps. Downstream control starts with bagging specimens for postage. At this point, the absence of a sample bottle or any incomplete or incorrect labeling should be noted. In case of inconsistencies noted during unpacking of envelopes, sorting sample bottles and request forms, or trimming specimens in order to fit them in tissue cassettes, such as differences between the specimen in the bottle and a sketch on the request form, the submitting clinician should be contacted immediately. If inconsistencies between clinical data and histopathologic findings are noted at the microscope, the preceding and subsequent slides should be checked for another corresponding inconsistency that suggests a mix-up of specimens. If no corresponding inconsistency is found, slides and paraffin blocks should be compared in order to exclude the error most easy to detect, namely, use of a wrongly labeled slide. Once the identity of the specimen on the slide and in the paraffin block has been confirmed, all specimens of the same submitting clinician of the same day should be checked for inconsistencies. If no other inconsistency is found, the reasons for the incongruity between clinical data and histopathologic findings can sometimes be clarified by consultation of the submitting clinician. When studying sections of tissue and dictating reports, histopathologists should not only check routinely the identity of numbers on slides and request forms, but also the names of patients on request forms and in the computer in order to detect keyboard entry errors.

The secretaries typewriting reports should notice inconsistencies in them, such as discrepancies between the dictated

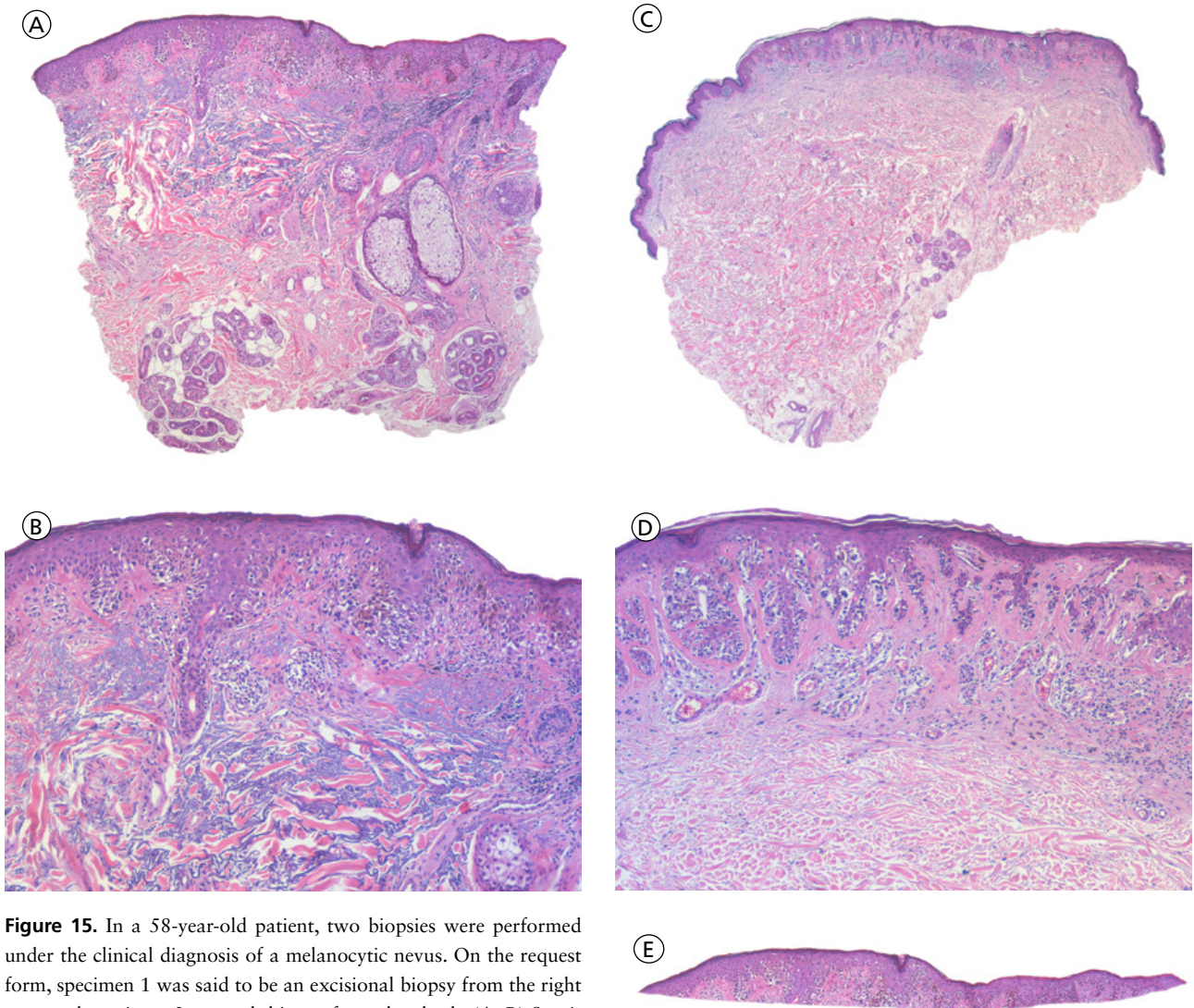
report and data on the request form (e.g., a computer code for an inflammatory dermatosis in a specimen suspected to be a neoplasm clinically; attestation of complete removal in a biopsy declared as incomplete) or contradicting statements (e.g., “no evidence of malignancy” in a basal-cell carcinoma; “complete removal” together with a note that the neoplasm extends to one lateral margin). Ideally, computerized systems should include a barrier for unusual or incompatible combinations of codes [26]. However, because elaborate computer systems for pathology laboratories with such functions are currently not available, control still depends mostly on the vigilance of the individuals involved, namely, secretaries and histopathologists. The latter should read typewritten reports and check them for mistakes before approving them by signature. The last link in the chain of downstream control is the clinician who should call the histopathologist in case of incongruities between the pathology report and the clinical picture.

When errors are noted in the chain of downstream control, they should be corrected immediately. Any error that is allowed to persist may be missed later on and may result in an incorrect report. Severe mistakes rarely result from a single error but typically from a combination of “latent” and “active” errors [26]. Even if the precipitating error is relatively trivial, e.g., correct designation but inverse listing of two biopsy specimens on a request slip (specimen 2 being listed above specimen 1), it should be corrected by filling out a new request form or by at least highlighting the inverse sequence by an eye-catching warning sign. Any “latent” error corrected early on reduces the risk of more serious errors following it.

## Clues for control

The chain of downstream control is the most expedient mechanism to detect and correct errors in the biopsy pathway. However, it can only work if appropriate clues are provided in preceding work steps that allow inconsistencies to be detected later on. For example, the size and shape of biopsy specimens should be documented in the laboratory before dissecting specimens in order to fit them into tissue cassettes. If this is done, a subsequent mix-up can be detected by comparing those data with the histopathologic section on the slide. The precise way in which specimens are dissected should also be documented in order to enable technicians to note a missing or superfluous piece of tissue when preparing paraffin blocks. Moreover, by describing precisely the size and shape of the obtained biopsy specimen to the submitting clinician, a mix-up of specimens in the clinic or medical practice can often be verified. Unfortunately, the latter option is being curtailed progressively by the ever-increasing number of very small and shallow shave biopsies. The specimens obtained by such biopsies usually cannot be told from one another. Moreover, very small and narrow biopsy specimens preclude recognition





**Figure 15.** In a 58-year-old patient, two biopsies were performed under the clinical diagnosis of a melanocytic nevus. On the request form, specimen 1 was said to be an excisional biopsy from the right arm, and specimen 2 a punch biopsy from the cheek. (A, B) Specimen 1 shows a punch biopsy of a melanoma in situ characterized by a proliferation of single melanocytes, many of which are present in the upper reaches of the epidermis. The dermis shows marked solar elastosis and a large sebaceous gland. (C, D) Specimen 2 shows the compound stage of a Clark's nevus. The lesion is symmetrical and sharply circumscribed, melanocytes are distributed in regular fashion, and there are no melanocytes in the upper reaches of the epidermis. There is no solar elastosis. The lesion does not extend to lateral margins. Those two specimens have been mixed-up. This can be concluded from type of excision (complete for the nevus, incomplete for the melanoma), the anatomy (the large sebaceous gland in Figure 15A indicates the cheek as the biopsy site), and the association of the melanoma with marked solar elastosis (also indicating the cheek as the biopsy site). Without the precise information on the request form, the mix-up of specimens would not have been detected. (E) Even with this information, the mix-up would not have been detected in the case of a superficial shave biopsy including only epidermis and papillary dermis, but not the sebaceous gland and the pronounced solar elastosis in the upper reticular dermis. [Copyright: ©2014 Weyers.]

of a mix-up on the basis of anatomical characteristics, such as sebaceous glands, apocrine glands, or solar elastosis, because those characteristics are often not exposed.

The most important clues for downstream controls are provided by clinical information on the request form. The more comprehensive that information, the greater is the likelihood to detect a mix-up of specimens. Among data that should never be omitted are at least one clinical diagnosis, a statement concerning the biopsy site without which a deviating anatomy cannot be noted, and a statement concerning the biopsy technique, such as shave, curettage, or punch (Figure 15A-E).

Completing the request form is an important task that should be carried out by the physician him- or herself. If it is delegated to an inexperienced assistant who does not understand the importance of those entries, the latter are often incomplete or wrong, such as the diagnosis of psoriasis in a biopsy for basal-cell carcinoma only because the patient also suffers from psoriasis and that diagnosis is the first to be mentioned in his file. If such misinformation is provided repeatedly by a particular medical practice or clinic, the histopathologist will eventually seize to inquire about discrepancies between clinical and histopathologic diagnoses,



**TABLE 1. Mix-up of specimens in the medical practice/clinic**

	Source of error	Prevention of error	Detection of error
1	Missing or incorrect data of patients on sample bottles or request forms	<b>Laboratory:</b> Complete removal of old adhesive labels and thorough cleaning of sample bottles before re-use of them <b>Practice:</b> Mention principally of name and date of birth of patients on both, sample bottles and request forms; use of bar codes to prevent transcription errors; legible labeling of vials and request forms (including clinical diagnosis, site of biopsy, mention of previous biopsies with corresponding pathology number) immediately after the surgical procedure; removal of completed vials and request forms before calling in the next patient; separation of the file of the current patient from other files; heightened attention in the case of patients with similar or identical names	<b>Practice:</b> Control of sample bottles and request forms after every surgical procedure; labeling of bottles and request forms in accordance with the sequence of biopsies; control of correct labeling of sample bottles and request forms before bagging them for postage <b>Laboratory:</b> Recognition of discrepancies between the specimen in the bottle and the description of it on the request form (e.g., shave, punch); immediate consultation of submitting clinicians in the case of inconsistencies or missing data on bottles or request forms
2	Incorrect correlation of sample bottles and request forms; missing or incorrect numbering of bottles containing biopsy specimens from the same patient	Deposition of sample bottles from the same patient in a defined unchangeable sequence during the biopsy procedure; labeling of bottles and request forms immediately after the biopsy by the surgeon him- or herself; use of attaching labels for labeling bottles instead of marker pens; labeling of bottles and request forms with Arabic instead of Roman numerals	<b>Histopathologist:</b> Recognition of discrepancies between clinical data and anatomical/histopathologic findings; in case of an inconsistency control of all biopsy specimens submitted by the same clinician for a corresponding inconsistency; in case of missing previous biopsies control of personal data of the patient by use of different variables (e.g., forename, surname, date of birth) to detect transcription mistakes
3	Loss of biopsy specimens/sample bottles	Control of the content of sample bottles before the cover is screwed down; secure fastening of the cover to prevent leakage of formalin; several bottles with specimens from the same patient always in the same envelope	

and the chances to detect a mix-up of specimens will decrease substantially. Completeness and correctness of information provided on the request form, however, is not enough; that information must also be legible. There is a peculiar tendency among literate human beings to write less legibly in the case of uncertainty about what is being written. However, if a clinician is not sure about a diagnosis in a difficult case, undecipherable information on a request form does not contribute to resolving the conundrum. If previous biopsies exist of a given lesion or disease, they should be mentioned specifically with reference to the previous pathology number. Commonly, entries concerning the same biopsy site differ from one another, such as “paranasal” and “cheek” for the very same spot, thus preventing the histopathologist from appreciating the identity of a lesion in the primary biopsy

and the re-excision. Abbreviations that are not generally used or whose meaning is ambiguous (e.g., “SK” for solar or seborrheic keratoses; “LP” for lichen planus or lymphomatoid papulosis) should be omitted on request forms.

Poor or missing communication among different health care providers is one of the greatest problems in the medical system. Unfortunately, the pressure of work is so high that poor communication is often accepted tacitly [32]. In the practice of dermatopathology, missing, incomplete, or illegible entries on request forms are so common that systematic inquiries for every case are impossible considering the sheer mass of deficient forms. If deficient request forms were exceptional, inquiries for additional information would be much more common. The lack of inquiries, in turn, contributes to the perception of filling out request forms as a cumbersome

**TABLE 2. Mix-up of specimens in the laboratory**

	<b>Source of error</b>	<b>Prevention of error</b>	<b>Detection of error</b>
1	Incorrect correlation of sample bottles and request forms after unpacking envelopes	<i>Practice:</i> Several bottles with specimens from the same patient always in the same envelope <i>Laboratory:</i> Deposition of sample bottles on top of the corresponding request form before numbering bottles and request forms; use of type-written pathology numbers and corresponding bar codes for labeling bottles and request forms; never unpacking several envelopes at the same time	<i>Histopathologist:</i> Recognition of inconsistencies between clinical data and anatomical/histopathologic findings; in case of inconsistencies control of previous and subsequent slides and of all specimens of the same submitting clinician for other inconsistencies suggesting a mix-up
2	Loss or confusion of pieces of tissue during dissection of specimens or in the tissue processor	Trimming of only a single specimen from the moment it is taken out of the sample bottle to the moment the tissue cassette is closed and put in the basket of the tissue processor; regular cleaning of pincers and scalpels in order to prevent adhesion of fragments of tissue to them; cleanliness in the laboratory and a floor of a light, uniform color in order to facilitate recovery of pieces of tissue that have fallen down; enwrapping of very small pieces of tissue in filter paper in order to prevent them from falling through tiny holes in the tissue cassette	<i>Laboratory:</i> Comparison of a sketch of the specimen and the way it was dissected with the shape and number of fragments of tissue when embedding them in paraffin
3	Use of a tissue cassette with a wrong number after dissection of specimens with a scalpel	Clear arrangement of both, sample bottles and pre-numbered tissue cassettes, in numerical sequence; control of numbers on the sample bottle, the request form, and the tissue cassette before dissecting specimens; enhanced care if additional tissue cassettes are needed for a single specimen (prevention of transcription mistakes such as transposed digits when labeling those cassettes)	<i>Histopathologist:</i> Recognition of inconsistencies between clinical data and anatomical/histopathologic findings; if portions of tissue have not been processed and embedded, comparison of them with the pieces of tissue in the paraffin block; histopathologic examination of tissue that has been left in the sample bottle
4	Transfer of tissue into the a wrong block when embedding specimens in formalin	Clear arrangement of both, tissue cassettes and pre-numbered blocks, in numerical sequence; control of numbers on the tissue cassette and the block before embedding specimens in paraffin; regular cleaning of pincers to prevent adhesion of fragments of tissue to them	<i>Histopathologist:</i> Recognition of inconsistencies between clinical data and anatomical/histopathologic findings; recognition of pieces of tissue that do not correspond to other pieces of tissue on the same slide
5	Transfer of tissue onto the wrong slide when cutting specimens at the microtome	Clear arrangement of both, paraffin blocks and pre-numbered slides, in numerical sequence; control of numbers on the block and the slide before clinching the block to the microtome and cutting sections; cleaning and change of the knife of the microtome at regular intervals; clean water bath to prevent “floaters”	<i>Laboratory:</i> Comparison of size and shape of the sections of tissue on slides with the pieces of tissue in paraffin block before slides are forwarded for microscopy <i>Histopathologist:</i> Recognition of inconsistencies between clinical data and anatomical/histopathologic findings; in case of inconsistencies comparison of sections of tissue on the slides with those in paraffin blocks

**TABLE 3. Mix-up of specimens at the microscope**

	Source of error	Prevention of error	Detection of error
1	Confusion of slides when taking them from the tray	<p><b>Laboratory:</b> Meticulous control of the correct sequence of slides and request forms before slides are forwarded for microscopy; indication of breaks in the regular sequence by place holders for missing slides and an eye-catching marker for additional slides on the same biopsy specimen</p> <p><b>Histopathologist:</b> Control of the numbers on the slides and request forms before dictating a report; care not to grab and put aside two request forms instead of a single one after dictation; heightened attention in the case of several slides on the same biopsy specimen; heightened attention following an interruption (e.g., by a telephone call)</p>	<p><b>Histopathologist:</b> Recognition of the missing concordance between pathology numbers on slides and request forms when checking those numbers prior to a new dictation or on the basis of inconsistencies between clinical data and histopathologic findings; control of a series of preceding slides, request forms, and dictations in order to detect the point of deviation</p> <p><b>Secretary:</b> Consultation of the histopathologist in the case of inconsistencies between clinical data and the histopathology report</p> <p><b>Practice/clinic:</b> Consultation of the histopathologist for clinico-pathologic correlation</p>
2	Confusion of request forms	Habitual palpation of the paper of the request form to make sure that only one request form is taken from the pile and put aside after dictation of a report; heightened attention in the case of paperclips that may catch another, unrelated request form	
3	Slip of the tongue when dictating a computer code	Use of redundant codes; elimination of codes that can be confused easily because of similarities phonetically or in typeface	

and negligible duty. Thus, deficiencies in communication are deepened structurally. However, structural deficiencies need to be addressed because they can be remedied much easier than individual human errors [33].

## Pitfalls

Individual errors caused by a short moment of abstraction of one of many persons involved in the biopsy pathway are unavoidable, considering the high number of patients managed day after day in medical practices and clinics and the enormous mass of biopsy specimens obtained. Full concentration of all involved persons at all times is a desirable but unrealistic demand. Concentration can be fostered, e.g., by sufficient rest periods and a quiet workplace. Any abstraction, e.g., by loud conversation within earshot, diminishes concentration and may lead to mistakes. Conversation, however, is essential for cooperation in a team. Interruptions, e.g., by telephone calls, are also unavoidable and contribute to the quality of service. Unnecessary interruptions concerning problems that could also be discussed at another time,

however, should be avoided. Any interruption is a potential source of error [27]. Because short-term memory is a particularly fallible human faculty, requirement for it should be minimized [26]. In case of an interruption, work should not be stopped in the middle of a procedure, such as dictation or typewriting of a report, but should first be finished before responding to the new request, and doubled care is necessary when resuming work, e.g., by renewed control of the name of the patient and of the pathology number on the slide and request form.

In addition to interruptions, there are other pitfalls in the biopsy pathway that should be known and respected, including similar or identical names of patients and deviation from the regular ascending sequence of pathology numbers. Any empty space on a tray bears the risk that a slide is put back at a wrong position and the subsequent slide being grabbed does not correspond to the next request form. Yet another pitfall is paperclips that attach some additional information to a request form. If such paperclips catch another request form, more than one form may be put aside after dictation, and the next report may be issued erroneously for the wrong patient.



**TABLE 4. Mix-up of specimens by the secretary**

	Source of error	Prevention of error	Detection of error
1	Entry of the data of the patient on a wrong pathology number	Use of a bar-code system for the entry of data; piling of request forms on top of one another so that only the uppermost one is visible, but never side to side; control of the pathology number and the patient's name prior to any new entry; heightened attention after interruptions (e.g., telephone calls)	<p><b>Histopathologist/secretary:</b> Comparison of data on the request form and in the computer before any dictation/entry</p> <p><b>Histopathologist:</b> Control of clinical and histopathologic diagnoses before approval of reports</p> <p><b>Practice/clinic:</b> Consultation of the histopathologist in case of inconsistencies between clinical findings and the histopathologic diagnosis</p>
2	Typewriting of a report on a wrong pathology number		
3	Entry of a wrong computer code	Use of redundant codes; elimination of codes that can be confused easily because of similarities phonetically or in typeface	

Safety measures designed to prevent or detect a specimen mix-up cannot always be implemented. For example, consultation of the submitting clinician in the case of an incompletely labeled specimen is only possible if the clinician can be reached. Not uncommonly, all attempts at reaching clinicians are wrecked by a busy signal of the telephone. Simultaneous control in the most vulnerable phases of the biopsy pathway may not be feasible in the case of an extraordinarily high workload or an unexpected shortage in personnel. The quality of downstream control depends not only on clues provided in preceding work steps, but also on the attentiveness and experience of the involved individuals and on the amount of stress under which they operate. Most errors occur on days with a high workload [4]. The opposite extreme, a very low workload, is also error-prone because boredom leads to poor performance. Performance is best at moderate levels of arousal [26].

## Documentation of errors

If errors are uncovered, they should not only be corrected but also documented. Documentation of errors heightens the awareness of problems and offers the chance to expose and resolve recurrent sources of error. In institutes with a formal plan for handling errors, errors are less common [29]. Errors should be classified according to type and probable place of occurrence (e.g., labeling sample bottles in the medical practice, unpacking and numbering specimens in the laboratory, examining slides at the microscope). Systematic documentation of errors in the computer facilitates analysis of them [4]. For an efficient analysis of errors, open handling of them in a matter-of-factly fashion without fear is indispensable. When errors are uncovered, the crucial question is not who was responsible for them, but why mechanisms for preventing them have failed [32]. Documentation should not

be restricted to severe errors with possible or real dramatic consequences but should also include minor errors because analysis of them reveals clues to prevent errors that are more serious [4]. This was already emphasized by the American industrial safety pioneer, Herbert William Heinrich, who emphasized that for every industrial accident that causes a major injury, there are 29 accidents that cause minor injuries and 300 accidents that cause no injuries [34].

A similar relationship can be assumed for “accidents” in the biopsy pathway. For every mix-up of specimens detected, many other mix-ups probably go unnoticed, and the vast majority of them do not cause any harm. In individual cases, however, consequences may be dramatic. Therefore, knowledge of sources of error, appreciation of dangers associated with them, precautions to prevent them, mechanisms of control to detect them, a clear structuring of the work flow in the biopsy pathway, and the possibility to prove a mix-up in the case of suspicion are crucial factors to safeguard the quality of medical care (see Tables 1, 2, 3, 4).

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