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Incidents in Molecular Pathology

Frequency and Causes During Routine Testing

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• ***Context.***—**Errors in laboratory medicine could compromise patient safety. Good laboratory practice includes identifying and managing nonconformities in the total test process. Varying error percentages have been described in other fields but are lacking for molecular oncology.**

Objectives.—**To gain insight into incident causes and frequency in the total test process from 8 European institutes routinely performing biomarker tests in non-small cell lung cancer and colorectal cancer.**

Design.—**All incidents documented in 2018 were collected from all hospital services for pre-preanalytical entries before the biomarker test, as well as specific incidents for biomarker tests.**

Results.—**There were 5185 incidents collected, of which 4363 (84.1%) occurred in the pre-preanalytical phase (all hospital services), 2796 of 4363 (64.1%) related to missing or incorrect request form information. From the other 822 specific incidents, 166 (20.2%) were recorded in the preanalytical phase, 275 (33.5%) in the analytical phase, and 194 (23.6%) in the postanalytical phase, mainly due to incorrect report content. Only 47 of 822 (5.7%) incidents were recorded in the post-postanalytical phase, and 123 (15.0%) in the complete total test process. For 17 of 822 (2.1%) incidents the time point was unknown. Pre-preanalytical incidents were resolved sooner than incidents on the complete process (mean 6 versus 60 days). For 1215 of 5168 (23.5%) incidents with known causes a specific action was undertaken besides documenting them, not limited to accredited institutes.**

Conclusions.—**There was a large variety in the number and extent of documented incidents. Correct and complete information on the request forms and final reports are highly error prone and require additional focus.**

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Errors in laboratory medicine could significantly compromise patient safety. According to the International Organization for Standardization (ISO) technical specification ISO/TS 22367:2008, all clinical laboratories must (1) implement measures to detect high-risk processes, (2) identify incidents and associated risks to patient safety, and (3) monitor the effectiveness of corrective actions.[1] Over the last decade, various studies have focused on estimating the percentage of different error types in several fields of laboratory medicine. The frequency of identified laboratory errors varies greatly, depending on the study design, country, laboratory procedures, and investigated steps of the total testing process (TTP). This TTP includes the preanalytical, analytical, and postanalytical phases, first referred to as the brain-to-brain loop by Lundberg et al.[2]

A ranging error percentage has been described in clinical biochemistry, hematology, and immunology of 0.1% up to 36.8%, with a variable distribution of 45.5% to 89.6% errors in the preanalytical phase, 2.6% to 18.0% in the (intra-)analytical phase, and 7.7% to 47.0% in the postanalytical phase.[3–8] In forensic genetics, the postanalytical phase was reported to be the major source of erroneous results with 61.9% postanalytical problems of the total error rate of 0.5%.[9]

Over time, a reduction in the analytical error rate was reported due to improvements in the reliability and standardization of analytical techniques, reagents, and instrumentation, but also advances in information tech-

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nology, quality control, and quality assurance methods.[10] Focus thus shifted toward the initial and final steps of the TTP outside the laboratories' test scope as possible compromising factors of the total test integrity.[11] These steps are often referred to as the pre-preanalytical phase and post-postanalytical phase, with estimated error rates contributing to 12% and 5% of the total errors, respectively.[12]

Of the (pre-) preanalytical errors, incomplete request form completion has been one of the most frequently reported incidents.[4,5,13] Several elements were lacking or incorrect, such as the clinical information on previous medication,[14] contact details of the requesting physician,[15,16] or a mismatch of the received sample with the patient identification.[17]

On the other hand, nonadherence to predefined sample acceptance criteria was also frequently reported,[4,5,13] especially for blood sample collection. In the post-postanalytical phase, reported incidents included (1) an inappropriate response to the receipt, interpretation, and utilization of laboratory information by the clinician, (2) feedback from clinicians, or (3) feedback on test results by providers of external quality assessment (EQA) programs. Examples are an excessive turnaround time and unreported critical values in the final report.[5]

Despite these studies, no information is available yet on the distribution of incidents in the TTP from laboratories testing predictive biomarkers in molecular oncology. As these tests convey necessary information for the selection of an appropriate targeted therapy, errors could result in a denial or unnecessary delivery of these therapies to cancer patients. Medical laboratories performing these tests are recommended to apply for ISO 15189:2012 accreditation.[18] This standard specifies that laboratories should (1) implement a documented procedure to identify and manage nonconformities in any aspect of the quality management system and for all TTP phases, (2) determine the root causes of these nonconformities, (3) take action to eliminate the cause(s), and (4) perform a risk analysis on the impact on patient safety.[18]

A recent study on the management of EQA results in metastatic colorectal cancer (mCRC) and non-small cell lung cancer (NSCLC) revealed that incorrect outcomes occurred throughout the different test phases. More specifically, of the 514 cases, 92 (17.9%) occurred in the preanalytical phase, 166 (32.3%) in the analytical phase, 226 (44.0%) in the postanalytical phase, and for 30 (5.8%) cases the exact time point was unknown.[29] Also, underlying error causes varied largely on the tested biomarker and applied analysis techniques. For these problems, many laboratories reported that they did not initiate any corrective or preventive actions (CAPAs), an observation that also occurred in accredited institutes.[29] As EQA programs send precut and prelabeled samples, several pre-preanalytical processes cannot be studied, such as the test request, sample reception and data entry, and sample preparation.

This study aimed to provide an overview of root causes and distribution throughout the TTP of documented incidents in 2018 by 8 clinical institutes routinely performing biomarker tests in NSCLC and mCRC.

MATERIALS AND METHODS

Eight institutes were included in this cross-sectional study, comprising 4 Belgian laboratories and 4 other European laboratories for comparison (Denmark, France, Slovenia, and the United Kingdom). The institutes were selected based on (1) our contacts in a larger project of biomedical sciences student internships, (2) on the delivery of routine biomarker testing for targeted therapy selection in NSCLC and mCRC, (3) on the possibility of providing an export of the documented incidents, and (4) on the institutes' availability during the study period. Institutes that did not perform molecular oncology tests for NSCLC and mCRC or did not keep any incident records were excluded. As ISO 15189:2012[18] accreditation is obligatory in Belgium for reimbursement of the performed analyses, all Belgian laboratories were accredited, compared with 2 of 4 European institutes. An overview of the institutes' characteristics (country, accreditation, setting, number of samples tested, number of people involved, average turnaround time, etc), and collected data (software for incident reporting, number of incidents documented, and type of information provided) is shown in Table 1.

From these institutes, all incidents that were routinely documented in a time period between January 1, 2018 and December 31, 2018 were collected and analyzed. Incidents in this manuscript are defined as follows: "all non-conformities, adverse events, or deviations from the standard operating procedure, occurring throughout all test phases, and identified in any way (including clinician complaints, internal quality control indications, instrument calibrations, checking of consumable materials, interlaboratory comparisons, staff comments, reporting and certificate checking, laboratory management, reviews, and internal and external audits)."

Incidents related to the pre-preanalytical phase (from the clinical question up to the test request, sample reception and entry) were collected at all hospital services because many of the laboratory information systems (LIS) do not discriminate between incidents at different services at this stage (the database for incident collection can be integrated into or separate from the laboratory information system, therefore when referring to the term LIS in this manuscript we refer to the database used for incident registration). From there on in the TTP (ie, from the preanalytical to the post-postanalytical phase), collected incidents were specific for performed biomarker tests in NSCLC and mCRC. The collected data were anonymized for patient information, and an additional nondisclosure agreement was signed with the institutes to safeguard the confidentiality of any medical or personal data that were still visible. These data were checked for completeness by the institutes and once more before analysis. All collected data were combined and blinded for the institute. Names of staff members who reported the incidents were replaced by their appropriate function in the laboratory for an objective comparison. Documented incidents were further categorized depending on the time point of occurrence (phase in the TTP), their causes, and actions undertaken. Frequencies and cross tabulations were used to summarize descriptive statistics. For this type of work, no institutional review board approval was needed at our institution.

RESULTS

In total, 5185 incidents were collected, of which 4363 (84.1%) occurred in the pre-preanalytical phase comprising all hospital services. For the other 822 collected incidents, which were specific for biomarker testing in NSCLC and mCRC, 166 (20.2%) were recorded in the preanalytical phase, 275 (33.5%) in the analytical phase, 194 (23.6%) in the postanalytical phase, and 47 (5.7%) in the post-postanalytical phase. Another 123 of 822 incidents (15.0%) concerned the complete TTP (infrastructure or documentation, etc) and for 17 (2.1%) incidents the exact time point in the TTP was unknown.

The exact phase and time point of occurrence for the collected incidents is shown in Figure 1, except for 17 incidents for which the time point was unknown. During the pre-preanalytical phase, 2796 of 4363 (64.1%) incidents were reported during the test request (ie, filling of the

Table 1. Characteristics and Collected Incidents From the 8 Institutes Included in the Study

Institute	1a	1b	1c	1d	2	3	4	5
Accreditation	Yes, ISO 15189:2012[18]	Yes, ISO 15189:2012[18]	Yes, ISO 15189:2012[18]	Yes, ISO 15189:2012[18]	No, national accreditation standard only	Yes, ISO 15189:2012[18]	Yes, ISO 15189:2012[18]	No, hospital accreditation only
Setting	University hospital	University hospital	University hospital	Community hospital	Community hospital	University hospital	University hospital	University hospital
No. tissue samples tested/year for common biomarkers in NSCLC								
ALK (NSCLC)	>1000	115	500–1000	100–250	/	10–50	>1000	250–500
ROS1 (NSCLC)	>1000	500–1000	500–1000	/	/	10–50	>1000	250–500
PD-L1 (NSCLC)	100–250	250–500	250–500	100–250	242	60	>1000	500–1000
EGFR (NSCLC)	250–500	337	500–1000	10–50	60	520	>1000	772
MET (NSCLC)	250–500	/	250–500	/	3	250	/	5
BRAF (NSCLC or mCRC)	250–500	100–250	500–1000	10–50	300–500	220	250–500	53
KRAS (NSCLC or mCRC)	250–500	250–500	500–1000	10–50	300–500	180	>1000	718
NRAS (mCRC)	250–500	250–500	250–500	10–50	300–500	220	>1000	/
No. people involved in oncology biomarker testing[a]								
NSCLC	6–10	>20	11–15	15–20	6–10	6–10	>20	1–5
mCRC	16–20	>20	1–5	1–5	11–15	6–10	16–20	/
TAT for clinical samples (average no. days)	8–14	1–7	8–14	1–7	1–7	8–14	1–7	1–7
Samples received from								
Internal pathologist		x	x		x	x	x	x
External pathologist	x	x	x			x	x	x
Oncologist		x	x	x		x	x	x
Pulmonologist	x	x	x	x		x	x	
Incident database	SharePoint, Microsoft	DaVinci (Da Vinci Laboratory Solutions)	Pre-preanalytical in GLIMS (MIPS Diagnostic Intelligence), others in Vivaldi (Vivaldi)	Pre-preanalytical in DaVinci (Da Vinci Laboratory Solutions), others in ExpressPack (EPQ)	Qualiware (CGI)	Blue Medi Santé from Blue Kango	Incidents with CAPA in Qpulse5 (Ideagen), others in Excel sheet	LABEX (Premisa)
Incidents collected								
Pre-preanalytical	66	819	2748	528	12	7	183	/
Specific for NSCLC and mCRC	127	283	7	78	108	51	163	5

Abbreviations: *ALK*, ALK receptor tyrosine kinase; *BRAF*, B-Raf proto-oncogene; *EGFR*, epidermal growth factor receptor; ISO, International Organization for Standardization; *KRAS*, KRAS proto-oncogene; mCRC, metastatic colorectal cancer; *MET*, MET proto-oncogene; *NRAS*, NRAS proto-oncogene; NSCLC, non-small cell lung cancer; *PD-L1*, programmed death ligand-1; *ROS1*, ROS proto-oncogene 1; TAT, turnaround time.

The pre-preanalytical phase is defined as all steps from the test request until entering of the request in the laboratory system. A detailed overview of the registered data per institute is given in Supplemental Table 1. Country 1 (lab a, b, c, d): mandatory accreditation for test reimbursement, may follow national or international guidelines on markers to be tested. Country 2: ISO 15189 accreditation not mandatory, follows national guidelines for biomarker testing, reimbursement of tests by national health insurance. Country 3: mandatory accreditation, must follow national requirements on markers to be tested, reimbursement of tests by the national department of health. Country 4: accreditation not mandatory but necessary for test reimbursement, no national requirement on markers to be included. Country 5: certification (but not accreditation) is obligatory by ministry of health. Follows European recommendations for tested markers. Tests are reimbursed by pharma and controlled by national health insurance.

[a] Includes all members included in predictive biomarker testing for NSCLC and mCRC, such as the technician, molecular biologist, and pathologist.

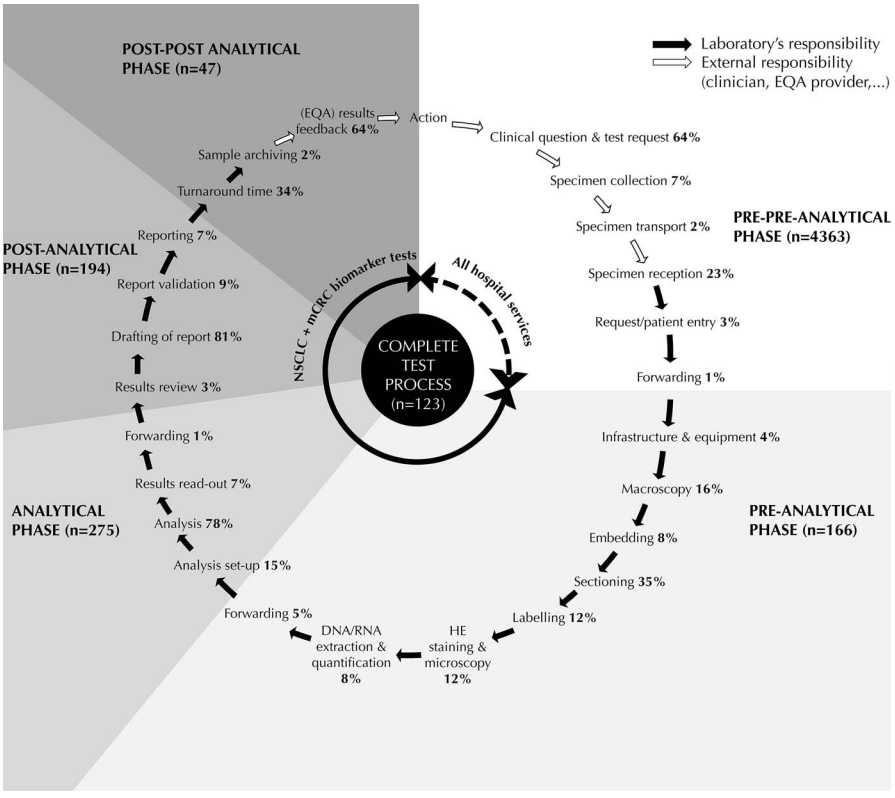

Figure 1. *Time point of incident occurrence in the total test process. Percentages represent the percentage of incidents being documented within their respective phase. Pre-preanalytical incidents were collected for all hospital services. Other incidents were specific for predictive biomarker testing in NSCLC and mCRC. Abbreviations: EQA, external quality assessment; H&E, hematoxylin and eosin; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer.*

request form), and 1008 of 4363 (23.1%) incidents during sample reception. Looking at the causes of the pre-preanalytical incidents, 2796 of 4363 (64.1%) were due to missing or incorrect information on the request form sent by the treating physician (Table 2). In more detail, (1) for 737 of 2796 (26.4%) incidents the clinical information (ie, previous patient history or acceptance criteria to perform the correct test) was lacking or incorrect, (2) the information for test reimbursement by the health insurance was missing in 557 of 2796 (19.9%) forms, or (3) the date of sample collection was absent in 552 of 2796 (18.7%) requests. For 1054 of 4363 (24.2%) incidents, the received sample material did not meet the laboratory's predefined acceptance criteria. This entailed an insufficient specimen amount or volume in 355 of 1054 (33.7%) cases, incorrect sample collection for 301 of 1054 (28.6%) incidents, or an absent/incorrect patient identifier for 222 of 1054 (21.1%) cases. For 352 of 4363 (8.1%) incidents, the material that was received did not match the description on the request form, in 251 of 352 cases (71.3%) because the form mentioned more or fewer specimens compared to the number of available samples.

The remaining 161 of 4363 (3.7%) pre-preanalytical incidents occurred when the material and request form were acceptable but were incorrectly entered in the LIS.

Looking at the biomarker-specific incidents in the other phases, incidents occurred most often during specimen sectioning (58 of 166 preanalytical incidents [34.9%]), the analysis itself (214 of 275 analytical incidents [77.8%]), drafting of the report (157 of 194 postanalytical incidents [80.9%]), and feedback on the results by the treating physician or EQA provider (30 of 47 post-postanalytical incidents [63.8%]) (Figure 1). Another 15 of 4363 (0.4%), 8 of 166 (4.8%), and 2 of 275 (0.7%) incidents occurred when forwarding the case for further processing to the next phase (Figure 1).

The underlying causes of NSCLC and mCRC specific incidents are presented in Table 3. The most frequent causes were sample switches in 35 of 166 (21.1%) preanalytical incidents, failed immunohistochemistry or fluorescence in situ hybridization tests in 42 of 275 (15.3%) analytical incidents, errors in the final report content of 152 of 194 (78.4%) postanalytical incidents, and documentation of EQA program results in 26 of 47 (55.3%) incidents of the post-postanalytical phase. For the 152 incidents on the report content, 44 (28.9%) reports had an incorrect test result or conclusion, 27 (17.8%) had an incorrect patient name or date of birth, and for 18 (11.8%) reports the time of validation occurred too soon or too late in the TTP. For the 123 incidents that affected the complete TTP, the necessary documentation or procedures were not kept in 39 (31.7%) issues, equipment maintenance was delayed in 20 (16.3%) incidents, and delayed document review was the basis for error in 13 (10.6%) incidents.

The incident causes were classified according to the relevant clauses of the ISO 15189:2012 standard and are depicted in Figure 2. Incidents with an unknown cause were excluded (17 of 5185) as well as pre-preanalytical incidents (4363 of 5185), as they were all related to clause 5.4, pre-examination processes. For the remaining 805 of 5185 entries, 107 of 805 (13.3%) were related to the standard's management requirements. In more detail, 42 of 805 (5.2%) were related to clause 4.3, document control, and 32 (4.0%) to clause 4.14, evaluation and audits.

The other 698 of 805 (86.7%) incidents were related to the technical requirements, in 198 of 805 (24.6%) cases for clause 5.3, laboratory equipment, reagents, and consumables, in 129 of 805 (16.0%) cases for clause 5.6, ensuring the quality, and in 126 of 805 (15.7%) cases for clause 5.8, reporting of examination results.

Table 2. Causes of Pre-Preanalytical Incidents Documented Across All Hospital Services

Causes of Pre-Preanalytical Incidents (N = 4363)	n	%
Information on the request form	2796	64.1
Clinical information absent or incorrect	737	26.4
Clinical info absent or incorrect (further unspecified)	466	63.2
Clinical acceptance criteria to perform the test missing	120	16.3
Clinical info form not attached to request form	92	12.5
Missing information about genetic counseling	28	3.8
Previous testing info necessary to perform the test lacking	28	3.8
Clinical info present, but unreadable	3	0.4
Information for reimbursement lacking	557	19.9
No date of collection present	522	18.7
No, incomplete or incorrect information about requesting physician or hospital	290	10.4
Sample type lacking or incorrect	261	9.3
No or incorrect test requested	149	5.3
No date of request present	105	3.8
Inconsistent or missing information (further unspecified)	94	3.4
Incorrect or absent patient name (first or surname or both)	35	1.3
Informed consent absent	24	0.9
Incorrect or absent date of birth	9	0.3
Incorrect sample localization mentioned	7	0.3
Incorrect/outdated request form template used	6	0.2
Sample acceptance criteria	1054	24.2
Insufficient sample material/volume received	355	33.7
Problem with sample collection	301	28.6
Heparin/EDTA/coagulant/citrate missing	161	53.5
Contamination of amniotic sample by maternal cells	66	21.9
Expired paper for blood spots used	53	17.6
Plasma not separated from debris	10	3.3
Incorrect sample collection (unspecified)	6	2.0
Sample not in correct tube type	5	1.7
No or incorrect patient identification/label on sample	222	21.1
Problem during sample transport	97	9.2
Delayed arrival of sample	44	45.4
Sample not frozen/on ice	24	24.7
Incorrect sample transport (unspecified)	16	16.5
Sample leakage/damage	13	13.4
Sample fixation/matrix suboptimal or incorrect (fresh versus FFPE)	61	5.8
Samples switched	18	1.7
Mismatch between request forms and received material	352	8.1
The number of received samples is more/fewer than those described on the request form	251	71.3
A request form was received without a sample	58	16.5
The sample label does not correspond to the identification on the form	20	5.7
A sample was received without a request form	12	3.4
The sample localization on the form does not match the material received	11	3.1
Processing of request form and order entry	161	3.7
Inappropriate test requested/forwarding to incorrect department/delayed processing of urgent sample	34	21.1
Incorrect or no patient name entered	31	19.3
Requesting service info not added or incorrect	28	17.4
Sample labeled incorrectly	20	12.4
Incorrect date of birth entered	11	6.8
Incorrect patient identification (file number, national registry number)	11	6.8
Incorrect sex entered	10	6.2
Booked in under incorrect sample type	10	6.2
Other	6	3.7

Abbreviations: EDTA, ethylenediaminetetraacetic acid; FFPE, formalin-fixed, paraffin-embedded; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer.

The pre-preanalytical phase is defined as all steps from the test request until entering of the request in the laboratory system, collected for all hospital services. Incidents specific for NSCLC and mCRC are presented in Table 3. The 6 unclassified incidents during processing of the request forms and order entry (category "other") consisted of an incorrect date of reception (1), problems with the automated infrastructure for scanning of the forms (2), a missing patient file (1), a further unspecified cause (2).

There was a wide variety in the number of documented incidents and recorded data per incident between the 8 institutes (Supplemental Table 1, see supplemental digital content containing 3 tables and 1 figure). One laboratory did not document pre-preanalytical incidents, while the other 7 institutes documented 7 to 2748 pre-preanalytical incidents in 2018. At 4 institutes, mainly analytical incidents were documented, with percentages ranging from 51 of 163 (31.3%) to 37 of 51 (72.5%). For 3 other institutes, the bulk of incidents occurred in the preanalytical, postanalytical, or complete TTP, respectively.

All institutes recorded the date of incident notification, the root case, and classified the incidents depending on the cause. Six laboratories mentioned the action plan, and 5 of them also evaluated the effectiveness of that plan. Other recorded elements were only documented by 2 institutes, such as the designated staff member for follow-up, the means of incident discovery, and how awareness was raised among the staff (Supplemental Table 1).

When comparing all incidents (with the exception of 17 of 5185 incidents with an unknown cause), for 3953 of 5168 (76.5%) incidents no immediate action was explicitly documented besides recording of the incident in the LIS for quality monitoring (Supplemental Table 2). In case a specific action was reported, the most frequent actions included contacting the requesting physician for 564 of 4363 (12.9%) pre-preanalytical incidents. Samples were retested for 27 of 166 (16.3%) preanalytical incidents, and for 62 of 275 (22.5%) analytical incidents. In the postanalytical phase report validation and correction were most often reported, for 83 of 194 (42.8%) cases.

In the post-postanalytical phase, 6 of 47 (12.8%) incidents were communicated to the staff for improvement and an

Table 3. Causes of Incidents Reported for NSCLC and mCRC Biomarker Testing

Incident Cause (N = 822)	n	%
Preanalytical	166	20.2
Samples switched	35	21.1
Incorrect or missing sample labels during cutting or DNA extraction	31	18.7
Sample microtomy problems (eg, incorrect protocol/tissue used, floaters, cut too deep, too thick, technical issues, etc)	29	17.5
Problem during sample embedding (eg, contamination, damage, multiple tissues in one block, etc)	17	10.2
Lost material	16	9.6
Equipment problems (errors, defects, dispensing of reagents, etc)	14	8.4
Accompanying H&E stain missing, bad quality, or incorrect	9	5.4
Inadequate amount of material for cutting/ extraction	8	4.8
Sample delayed between departments/ services	7	4.2
Analytical	275	33.5
Failed IHC or FISH test	42	15.3
Technical/server problems with autostainer or sequencer	44	16.0
Missing, inadequate, or expired reagents	39	14.2
Incorrect sample labelling/worksheet	28	10.2
Sample switch	17	6.2
Sample lost or not tested	16	5.8
Problem with procedure (unspecified)	11	4.0
Inadequate, failed, or lack of control tissue	21	7.6
Faint/too much background FISH/IHC signal	18	6.5
Incorrect test performed/procedure not followed	11	4.0
Insufficient/inadequate material to perform the test	9	3.3
Failed or incorrect sequencing run	7	2.5
Sample contamination	7	2.5
Other	5	1.8
Postanalytical	194	23.6
Report content	152	78.4
Incorrect result/conclusion on report	44	28.9
Patient information (name or date of birth) incorrect	27	17.8
Incorrect validation (too soon or too late) of report	18	11.8
Incorrect sample localization	15	9.9
Error in microscopy part (unspecified)	13	8.6
Incorrect or absent sample number on report, but correct result	13	8.6
Incorrect clinical history	7	4.6
Missing result on report	6	3.9
Incorrect report template used	3	2.0
Incorrect requesting physician mentioned	3	2.0
Incorrect author of report	3	2.0
Reports/results from patients switched	16	8.2
Software problem with automated result	13	6.7
No report present	6	3.1
Unexplained molecular result obtained	5	2.6
Documented procedure on reporting lacking	2	1.0
Post-postanalytical	47	5.7
Results of external quality assessment programs	26	55.3
Delayed turnaround time	16	34.0
Discrepant result reported by physician	4	8.5
Sample archiving	1	2.1
Complete TTP	123	15.0
Missing documentation or procedure	39	31.7
Maintenance/calibration not performed or too late	20	16.3
Documentation not reviewed in timely manner	13	10.6
Communication between services/ departments	10	8.1
Systematic review of CAPAs or quality indicators	8	6.5
Document changes/versions	8	6.5
Reagents/samples storage and handling	6	4.9
Validation procedures	6	4.9
Infrastructure/equipment	5	4.1
Access to laboratory information system	5	4.1
Costs and suppliers	3	2.4
Unknown	17	2.1

Abbreviations: CAPA, corrective/preventive action; FISH, fluorescence in-situ hybridization; H&E, hematoxylin and eosin; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; NSCLS, non-small cell lung cancer; TTP, total test process.

Phases are defined as follows: preanalytical phase, sample preparation to perform the test (embedding, sectioning, labelling, pathology review and/or DNA/RNA extraction); analytical phase, set-up of the analysis sheets and the actual biomarker test and results output; postanalytical phase, results interpretation and review until creation of the report; post-postanalytical phase; everything after release of the results, including participation to external quality control. Incidents in the complete process were general system or management requirements not related to any of the specific phases.

Incidents, such as sample switches or lost samples, could occur throughout the test process; hence, they are shown in the phase based on the time point of detection. Incidents are specific for NSCLC and mCRC, in contrast to incidents covering all hospital services reported in Table 2. The 5 unclassified incidents (category "other") in the analytical phase consisted of a delayed transfer between services (2), referral of analytical test to an external laboratory (1), limited working space for analysis (1), and a staff member being injured (1).

identical percentage (12.8%) were cases with a delayed result who were further finalized. An update of the documentation was the main action for 33 of 123 (26.8%) problems in the complete TTP.

For 1365 of 5168 (26.4%) incidents, the date of first registration and date of closure were both available. From these dates, the turnaround time was calculated, which ranged between 1 and 411 days. Of incidents, 1018 of 1365 (74.6%) were closed at the day of creation, and another 206 of 1365 (15.1%) were closed within the first month after creation. The average turnaround times were the lowest for pre-preanalytical incidents and highest for incidents affecting the complete test process, which are also considered the most severe (Supplemental Figure 1). For 532 of 5168 (10.3%) of these incidents, a deadline was included for the corrective action, which was reached in 478 of 532 (89.8%) incidents.

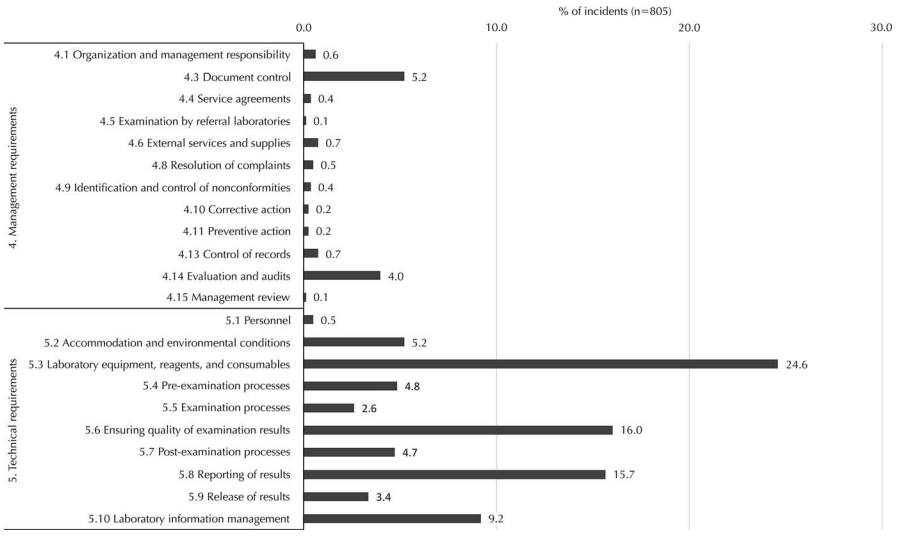

Figure 2. *Relation between incidents and corresponding ISO 15189:2012 clause. Only incidents specific for NSCLC and mCRC were shown. Of pre-preanalytical incidents from all hospital services, 4363 were excluded, as they were all related to clause 5.4: pre-examination processes. From the remaining 822 incidents, 17 were excluded as the exact cause was unknown and could not be linked to the ISO standard.[18] Abbreviations: ISO, International Organization for Standardization; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer.*

For 182 of 5168 incidents (3.5%), further follow-up was provided, for 113 of 182 incidents in the format of a specific preventive action, whereas for 91 of 182 incidents the effectiveness of the performed CAPA was verified (Supplemental Table 3).

Four of 8 institutes also performed a risk analysis on (a subset of) the documented incidents (n = 283) (Supplemental Table 1). Of these 4 institutes, 2 recorded the possible harm for patients in a descriptive manner (ie, by a sentence stating the possible risk), while the other 2 used a risk scale on a total of 3 or 20 points. Of the 283 incidents for which a risk analysis was available, 209 (73.9%) yielded no possible risk, 65 (22.9%) carried a limited-to-moderate risk, and 9 (3.2%) conferred a possible risk to the patient (Supplemental Table 3).

For 149 of 5168 (2.9%) entries, the channel through which the incident was initially detected was documented or could be deduced from the detailed description (Supplemental Table 3). Of those 149 incidents 84 (56.4%) were first identified during an audit, of which 6 (4.0%) by an external audit, 33 (22.2%) by an internal audit, and for 45 (30.2%) the audit type was unspecified. Another 26 of 149 (17.5%) incidents were discovered by participation to EQA programs, and 15 (10.1%) during management review. Twelve (8.1%) incidents were discovered during monitoring of the laboratory environment, evaluation of quality indicators, or an automatic incident system report. The remaining 9 (6.0%) and 3 (2.0%) incidents were staff suggestions and clinician's feedback/complaints, respectively.

The responsible staff members are shown in Figure 3, for incident registration (A) and follow-up (B). Information about the person who documented the incident was available for 1368 incidents (Figure 3, A), and for 1624 incidents the person responsible for follow-up was indicated (Figure 3, B). Of the 1368 incidents, 905 (66.2%) were reported by an administrative officer, in 784 of 905 (86.6%) of times due to the registration of pre-preanalytical incidents during sample reception. Only 8 (0.6%) incidents were reported by the laboratory director (Figure 3, A). Follow-up of the performed actions was carried out in 1279 of 1624 (78.8%) cases by the administrative officer also (Figure 3, B).

While the molecular biologist and other staff members (geneticists, nurses, or the requesting physicians) were involved in 52 of 1368 (3.8%) and 9 of 1368 (0.7%) of registered incidents, respectively (Figure 3, A), they were not

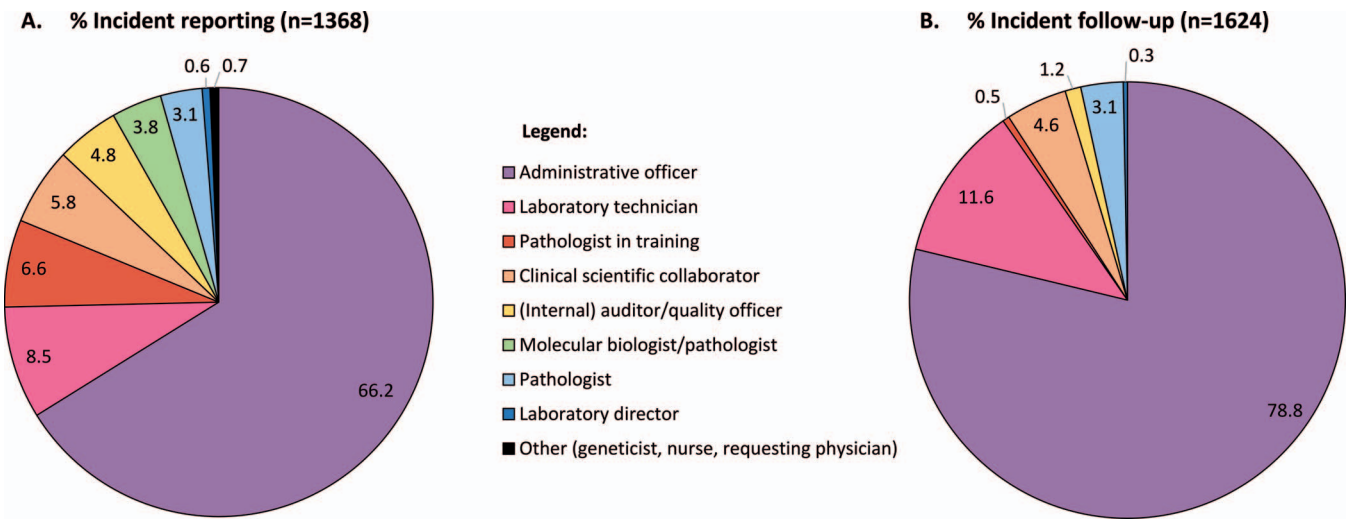

Figure 3. *Staff members involved in incident reporting (A) and follow-up (B).*

involved in further follow-up of the CAPAs to be undertaken (Figure 3, B).

DISCUSSION

Accurate predictive test results are indispensable for patient management. Laboratories are recommended to document errors and implement the necessary CAPAs to further improve their quality and eliminate recurring incidents.[19,20] The ISO 15189 standard requires documentation and review of incidents at regular intervals and participation in EQA programs to verify the laboratory's performance.[18] Even though previous studies in other fields reported on error management, there was a need to evaluate incidents in molecular oncology within the framework of the TTP.

Our analysis in 8 institutes performing routine diagnostic tests reveals that there is a wide variety in the number and extent of incidents recorded in the LIS. As the ISO 15189 standard requires that laboratories must have a documented procedure to identify and manage nonconformities in any aspect of the TTP,[18] there is a certain degree of freedom for laboratories to implement this according to their needs and within a specific software for further monitoring. In our study, 2 nonaccredited laboratories documented fewer incidents and less detailed information per incident (Supplemental Table 1); however, the number of incidents reported was highly variable within accredited institutes as well. An additional evaluation with a larger number of accredited versus nonaccredited institutes could be beneficial to evaluate practices of incident reporting related to accreditation status. Even though no evidence was provided for better incident management by accredited laboratories in this study because of the small number of nonaccredited institutes, the ISO 15189 standard provides a valuable framework for incident management. As such, laboratory accreditation according to this ISO standard is mandatory in some countries to perform these tests or receive test reimbursement.

For instance, laboratories in the United States are required to participate in accreditation programs by the College of American Pathologists to adhere to the Clinical Laboratory Improvement Amendments.[21] In this study, the institutes from Belgium, France, and the United Kingdom were accredited.

Many incidents in the accredited institutes were merely a notification of the incident without the necessity of performing a corrective action (as exemplified by the absence of immediate actions in Supplemental Table 2), but were analyzed internally as quality indicators.

Looking at all hospital services, we observed a large number of incidents still related to sample acceptance criteria and the accompanying request forms. This was found even in spite of template request forms and adequate instructions for sample collection and transport for the requesting services, which were available on the institutes' websites. This could be explained as the pre-preanalytical phase includes different stakeholders, which makes this phase more difficult to monitor,[22] such as the clinician, nurses, and others involved in patient identification, data entry, specimen collection, and transport. Also, more pre-preanalytical incidents were documented compared with previously reported studies with an error rate between 5% and 12%.[12] While those studies focused on this earliest phase as part of the TTP and for only 1 hospital service, pre-preanalytical incidents were analyzed separately in this study because they were collected at all hospital services (and not only for molecular pathology in NSCLC and mCRC). This separate analysis also explains the variation in pre-preanalytical incidents between institutes, as not all institutes offer the same diagnostic tests, even though their testing volume for NSCLC or mCRC biomarkers was comparable (Supplemental Table 1). In addition, the complexity of molecular analyses with several sample types, biomarkers, technique types, and assays makes the pre-preanalytical phase error prone. From the patient's viewpoint, the integrity of the entire process is important and errors in the earliest phases should be intercepted early on. As such, correct clinical context or patient identification are both necessary to appropriately report the findings and prevent sample switches. On the request form, at least a clear description of the clinical problem to be solved by molecular pathology should be adequately described. Also, sample acceptance criteria should be implemented in a laboratory. This allows a test to be performed under optimal conditions for its validated intended use, to avoid incorrect results in the further TTP.

Moreover, problems during test requesting and sample collection require extra measures (such as contacting the requesting physician or requesting a new sample) that could impose additional patient discomfort and delayed test results. Our findings are thus in line with previous studies, with high error rates at the pre-preanalytical stage, with incomplete request form filling and sample acceptance criteria as the most frequent causes.[4,5,13] Only 18.1% of previously reported total errors were internal to the laboratory, emphasizing the role of external causes particularly in the pre-preanalytical and post-postanalytical phases.[4] This is exemplified in our study where only 161 of 4363 (3.7%) of all pre-preanalytical incidents were due to incorrect entry of the received request in the system within the laboratory itself. Other studies highlighted incorrect sample collection as one of the main incidents, especially for blood sample tubes.[5,13] In this study, 242 of 1054 (22.9%) pre-preanalytical sample issues concerned an incorrect blood collection (4.7% of all analyzed incidents). While these incidents were collected for all hospital services (and thus not specific for NSCLC or mCRC), this is an important factor to consider for predictive biomarker testing. Namely, many institutes have started routine testing on liquid biopsies for the epidermal growth factor receptor (NM_005228.5) c.2369C>T p.(Thr790Met) variant in NSCLC, and standardization of the preanalytical conditions in this field is currently still a main concern.[23]

Besides the pre-preanalytical incidents, collection of the incidents in the subsequent phases revealed that the analytical phase was most error prone, followed by the postanalytical and preanalytical phases. While each phase presented its own specific problems, one major source of error in the postanalytical phase was the occurrence of incorrect report content (152 of 194 [78.4%]). Although a reduction in the analytical error rate was previously reported due to improvements in the reliability and standardization of analytical techniques,[10] we observed a higher incident rate at this phase compared with the preanalytical or postanalytical phases.

Many of these analytical problems were related to failed runs or unexpected software errors of the equipment for which the manufacturer was contacted. Indeed, the increased use of preprogrammed commercial test methods or

automatization might lead to a black box for which problems cannot easily be resolved by the laboratory staff. This is in contrast to previous findings, where causes for deviating EQA results in the analytical phase were mainly due to inadequate test sensitivity or variant coverage, or incorrect test interpretation, such as sequencing curves.[29] It is therefore highly recommended that laboratories participate to QA schemes, to confirm the quality of testing, data mining, and reporting the results. As EQA participation allows comparison to international peers, incorrect results can be identified that might not have been detected during routine incident reporting if technical problems are absent.

Adding to the complex test methodology is the wide range of specimen types examined in molecular diagnostic testing compared to other fields, such as fresh or formalin-fixed, paraffin-embedded tissue, blood, or cytologic preparations. Every specimen type requires correct test selection, creation of different workflows, specimen handling, and data management.[24] Moreover, there is a wide variety of predictive markers and recommended technique types, such as fluorescence in situ hybridization, immunohistochemistry, or (variant analysis by) massive parallel next-generation sequencing panels, or commercial test methods. This variety poses an additional challenge for reporting a correct and complete clinical history and request, but also for reporting multiple test results. In our study, the final report content was indeed highly error prone. Correct reporting in a clear and transparent format is important for the clinician to interpret the obtained results related to the patient context, sample limitations, and applied test methods. While several guidelines on reporting exist,[25] there is still debate on the necessary elements to be included according to the different intralaboratory and extralaboratory stakeholders.

Looking at the exact time point of incident detection (Figure 1), 1%, 5%, and 1% of incidents occurred when forwarding the sample to another service or department for further processing of the sample or for writing the report.

This stresses the importance of identifying frequencies and causes in the different phases, but also for continuous quality improvement throughout the TTP. With the increasing availability of next-generation sequencing to analyze multiple biomarkers in parallel, laboratory outsourcing is expected to increase, and hence designated professionals with experience in multiparallel data analysis will need to be involved. In this case, it remains the laboratory's own responsibility to ensure the quality of the final results. Previous studies demonstrated that laboratories who outsourced a part of the analysis were indeed more likely to have a lower performance in EQA schemes.[29] The impact of the laboratory framework and multiple transfer steps of an individual sample on laboratory quality should be looked into.

A small percentage (47 of 822 [5.7%]) of incidents were reported in the post-postanalytical phase, the majority concerning the results or availability of EQA programs, as well as delayed results in a routine setting. Only 4 of 47 (8.5%) incidents were detected based on feedback by the treating physician. A previous study on the follow-up of deviating EQA results already revealed that errors in later TTP phases are less likely to be noticed in advance by any of the quality checks implemented at regular time points in the TTP.[29]

Such incidents reported by the physician are important as they represent errors that were not noticed before releasing the results and could therefore harm patient safety.

Previously, the potential or actual harm of incidents on the patient population was estimated to range from 18% to 65%, depending on the field of interest.[4,9,13,26–28] In this study, a risk analysis was documented for only a small fraction of incidents. Of those 283 incidents, 9 (3.2%) included a possible or actual risk to the patient. It must be noted that we only evaluated documented incidents from the LIS, which were corrected before releasing the results or upon the clinician's feedback. When re-evaluating the documented incidents in the future, more post-postanalytical incidents might be observed in these institutes, owing to incidents that were not yet detected, but for which feedback might still be pending.

For instance, the requesting physician might contact the laboratory if the patient does not respond to the therapy as expected by the reported test outcome, which takes some time to be noticed. Unexpected patient response to treatment could be related to the intrinsic property of the patient's clinical context, but also to an incorrect test result. These incidents might be revealed sooner with the upcoming implementation of molecular tumor boards, during which patient's results are discussed together with the laboratory and treating physician. Deviating results might then be added directly to the patient's clinical record without the additional registration of the incident in the laboratory. On the other hand, with the large frequency of incidents being reported in the preceding phases, it might be that test results are in fact highly accurate and the recorded post-postanalytical incidents are actually scarce in routine practice. Incidents in the post-postanalytical phase and incidents affecting the complete process were less easily resolved, as they were often more fundamental and related to the lack of documented procedures. Also, the exact time point of these incidents requires an investigation, which may take additional time.

As a result of the incident, laboratories are required to define the immediate CAPAs.[18] Even though for 3953 of 5168 (76.5%) incidents no immediate actions were mentioned, recording of the incident for further evaluation of the quality policy at regular intervals is good practice in this case. For the other incidents, logical CAPAs were performed which most often included (1) to contact requesting physician in the pre-preanalytical phase, (2) retesting the sample for incidents in the preanalytical or analytical phase, (3) correcting the reports in the postanalytical phase, and (4) communication to staff members and updating the documentation for post-postanalytical and complete TTP incidents. Similar to the EQA scheme,[30] appropriate CAPAs were not limited to accredited institutes or those testing a larger number of samples annually for common biomarkers in NSCLC and mCRC.

Even though the institutes reported that the molecular biologist is actively involved in follow-up of the deviating EQA results,[30] none of the CAPAs were undertaken by the molecular biologist in this study. Also, it is not surprising that the laboratory director was only involved in a small percentage of incidents (Figure 3), as they are often reported by the staff member encountering them in the laboratory. However, the absence of these staff members in recording the CAPAs in the system does not exclude their involvement, as many incidents were discussed further via laboratory meetings or incidents reports (Supplemental Table 2).

To conclude, to our knowledge, for the first time in molecular oncology, this study analyzed incidents that are

useful for quality improvement, benchmarking, and contributing to an open attitude about incident reporting with the ultimate goal of improving patient safety. They highlight the importance of additional quality assurance when drafting the request forms and final reports, as well as of participation to EQA to reflect the variety in reporting in the individual countries.

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