Supplemental Digital Content, containing 1 figure and 3 tables.
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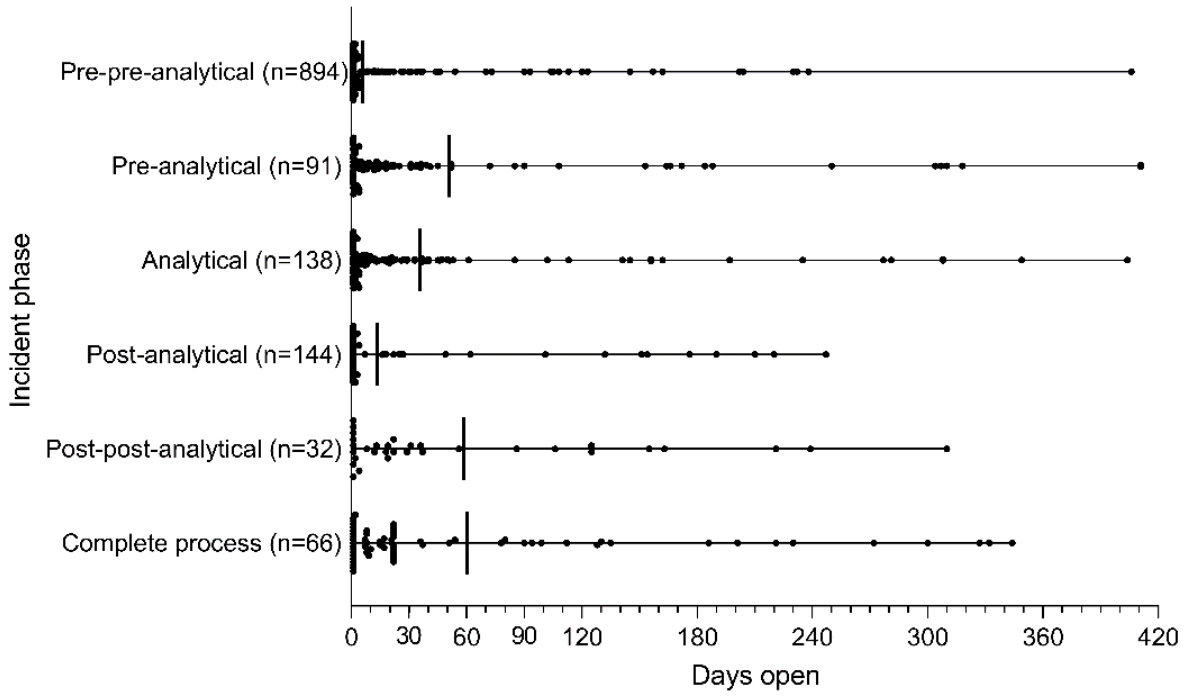
Supplemental figure 1: Number of days between incident reporting and closure.



Each dot represents the number of days a specific incident was opened. Horizontal lines show the range between the minimum and maximum number of days. Vertical lines represent the average days for all incidents within that phase. Phases were defined as: pre-pre-analytical phase, from the test request until entering of the request in the laboratory system; pre-analytical 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; post-analytical phase, results interpretation and review until creation of the report; post-post-analytical 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.

Supplemental table 1: Collected incidents from the eight institutes included in the study.

Institute n°	**1a**	**1b**	**1c**	**1d**	**2**	**3**	**4**	**5**
Accreditation	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	No, national accreditation standard only	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	No, hospital accreditation only
Incidents collected	193	1102	2755	606	120	58	346	5
Pre-pre-analytical (all hospital services)	66	819	2748	528	12	7	183	/
Specific for NSCLC & mCRC	127	283	7	78	108	51	163	5
Pre-analytical	*38 (29.9%)*	*40 (14.1%)*	*2 (28.6%)*	*9 (11.5%)*	*57 (52.8%)*	*4 (7.8%)*	*16 (9.8%)*	*/*
Analytical	*68 (53.5%)*	*75 (26.5%)*	*1 (14.3%)*	*8 (10.3%)*	*32 (29.6%)*	*37 (72.5%)*	*51 (31.3%)*	*3 (60.0%)*
Post-analytical	*11 (8.7%)*	*131 (46.3%)*	*2 (28.6%)*	*0 (0.0%)*	*1 (0.9%)*	*6 (11.8%)*	*41 (25.2%)*	*2 (40.0%)*
Post-post-analytical	*2 (1.6%)*	*22 (7.8%)*	*2 (28.6%)*	*6 (7.7%)*	*1 (0.9%)*	*4 (7.8%)*	*10 (6.1%)*	*0 (0.0%)*
Complete process	*8 (6.3%)*	*15 (5.3%)*	*0 (0.0%)*	*55 (70.5%)*	*0 (0.0%)*	*0 (0.0%)*	*45 (27.6%)*	*0 (0.0%)*
Unknown	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*17 (15.7%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
Hospital services for pre-pre-analytical incidents	Pathology (molecular, surgical, anatomic, incl. cytology and histology)	Pathology (molecular, surgical, anatomic, incl. cytology and histology)	Human genetics (including constitutional, prenatal and somatic genetic testing, cytogenetics, biochemical genetics)	Pathology (molecular, surgical, anatomic, incl. cytology and histology)	Molecular pathology (including genetics and immunohistochemistry)	Molecular pathology (biomarker tests for mCRC and NSCLC)	Molecular Pathology (biomarker tests for mCRC and NSCLC), Histopathology, Biochemistry, Haematology, Microbiology	Molecular pathology Biomarker tests for NSCLC only

Supplemental table 1: Collected incidents from the eight institutes included in the study. (*Continued*)

Institute n°	**1a**	**1b**	**1c**	**1d**	**2**	**3**	**4**	**5**
Accreditation	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	No, national accreditation standard only	Yes, ISO 15189:2012 [1]	Yes, ISO 15189:2012 [1]	No, hospital accreditation only
Registered data								
Date of registration/occurrence	x	x	x	x	x	x	x	x
Root cause	x	x	x	x	x	x	x	x
Classification by type	x	x	x	x	x	x	x	x
Unique incident identifier or hospital service where it occurred	x	x	x	x	x	x	x	
Phase/time-point of occurrence		x		x		x	x	x
Action plan	x	x	x			x	x	x
Short description (title)	x	x	x	x			x	
Check of efectiveness/improvement		x	x	x		x	x	
Staff member reporting the incident	x	x	x	x			x	
Status/date of incident closure	x	x	x	x			x	
Risk assessment or severity				x	x	x	x	
Target date		x		x			x	
Person responsible for the action		x	x				x	
Sample number	x				x			
Means of discovery	x						x	
Personnel update/meeting				x			x	
Clinical info: patient name or age, requesting physician, outpatient or inpatient		x			x			
Link to machinery, area/service of incident correction					x		x	

The pre-pre-analytical phase is defined as all steps from the test request until entering of the request in the laboratory system. 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. Abbreviations: ISO, International Organization for Standardization; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer.

[1.] International Organization for Standardization (ISO). ISO 15189:2012 Medical Laboratories—Particular Requirements for Quality and Competence. 2012: ISO, Geneva.

Supplemental table 2: Immediate actions reported for the observed incidents in the different test phases.

Pre-pre-analytical (n=4363)	**N**	**%**	**Information on the request form**	**Mismatch between request forms and received material**	**Processing of request form and order entry**	**Sample acceptance criteria**
No explicit data on immediate action present	3627	83.1	2294	251	126	956
Contact the requesting physician	564	12.9	439	70	6	49
Retrieve missing information from laboratory information system	49	1.1	48	0	0	0
Verify/correct the conclusions in the final report	30	0.7	2	20	8	0
Change the sample label	25	0.6	2	3	0	20
Correct test requested	17	0.4	7	0	8	2
Communicate to staff/laboratory meeting	12	0.3	1	3	8	0
Other	10	0.2	2	1	5	2
Verify the sample	10	0.2	0	2	0	8
Split the samples/delete the unwanted samples	9	0.2	0	2	0	7
Fixate the samples	7	0.2	0	0	0	7
Check the final report	3	0.1	0	0	0	3

Pre-analytical (n=166)	**N**	**%**
No explicit data on immediate action present	84	50.6
Retest the sample	27	16.3
Communicate to staff/laboratory meeting	11	6.6
Change the sample label	9	5.4
Check and/or correct the final report	9	5.4
Equipment maintenance	8	4.8
Verify the samples	6	3.6
Accept or add the correct test request	4	2.4
Update the protocol/procedure	3	1.8
Other	5	3.0
Analytical (n=275)	**N**	**%**
No explicit data on immediate action present	84	30.5
Retest the sample	62	22.5
Contact the manufacturer	31	11.3
Order new equipment or reagents	20	7.3
Verify the final report/result	17	6.2
Communicate to staff/laboratory meeting	14	5.1
Equipment maintenance	10	3.6
Update the protocol/procedure	6	2.2
Change the control tissue	5	1.8
Additional validation of reagentia	4	1.5
Other	22	8.0
Post-analytical (n=194)	**N**	**%**
Devalidate the report	83	42.8
No explicit data on immediate action present	61	31.4
Correct the report (results/conclusion)	25	12.9
Update or change the procedure	5	2.6
Communicate to staff/laboratory meeting	5	2.6
Change the sample label	4	2.1
Retest the sample	4	2.1
Other	7	3.6

Supplemental table 2: Immediate actions reported for the observed incidents in the different test phases. (*Continued*)

Pre-pre-analytical (n=4363)	N	%	Information on the request form	Mismatch between request forms and received material	Processing of request form and order entry	Sample acceptance criteria
Post-post-analytical (n=47)	**N**	**%**				
No explicit data on immediate action present	14	29.8				
Communicate to staff/laboratory meeting	6	12.8				
Transferred the case and finalized result	6	12.8				
Devalidate and correct the report	5	10.6				
Retest the sample	4	8.5				
Additional interlaboratory comparison	3	6.4				
Change protocol	3	6.4				
Other	6	12.8				
Complete test process (n=123)	**N**	**%**				
No explicit data on immediate action present	61	49.6				
Update or implement missing documentation	33	26.8				
Perform equipment calibration	9	7.3				
Monitoring quality indicators	6	4.9				
Equipment maintenance	4	3.3				
Other	10	8.1				

The 17 incidents for which the cause was unknown were excluded. In case 'no explicit data on the immediate action present' was reported, the action undertaken was documenting the incident in the laboratory system itself. Phases were defined as: pre-pre-analytical phase, from the test request until entering of the request in the laboratory system; pre-analytical 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; post-analytical phase, results interpretation and review until creation of the report; post-post-analytical 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.

Unclassified actions (category 'other') included: **information on the request form**, update instructions (1), change the clinical info (1); **mismatch between request and material**, new request form created (1); **processing order**, revise instructions/optimize communication for sample collection (2), change procedure (1), contact IT (1), contact pathologist (1); **sample acceptance criteria**, ask help from other department (1), new request form created (1); **pre-analytical phase**, change the reagents (2), contact the manufacturer (1), perform a risk assessment (1), melt sample to have additional material (1); **analytical phase**, check samples (3), logging the problem/root analysis (3), request the correct test (3), staff training (3), contact requesting physician (2), resolve manually (in case of equipment failure) (2), second opinion/involve an additional staff member (2), unknown (2), relocate samples (1), automatization (1); **post-analytical phase**, root cause analysis (3), contact IT/manufacturer (2), contact requesting physician (2); **post-post-analytical phase**, additional equipment included (2), revalidation (2), contact IT (1), equipment maintenance (1); **complete test process**, contact IT/manufacturer (2), order new material/reagents (2), communicate to staff (1), complete training (1), correct number (1), planned audit (1), relocate samples (1), retest samples (1). Abbreviations: N, Number.

Supplemental table 3: Channel for incident detection, estimated incident risk, and follow-up of CAPA effectiveness.

	Number of incidents (N=5168)	% incidents
Incident detection	**149**	**2.9**
Audit	84	56.4
Unspecified	*45*	*53.6*
Internal audit	*33*	*39.3*
External audit	*6*	*7.1*
External quality control	26	17.4
Management review	15	10.1
Staff suggestion	9	6.0
System printout	5	3.4
Environmental monitoring	5	3.4
Clinician's feedback, complaint	3	2.0
Quality indicators	2	1.3
Incident risk analysis*	**283**	**5.5**
Risk classification	283	100.0
Descriptive manner (2 institutes)	*179*	*63.3*
3-point scale (1 institute)	*58*	*20.5*
20-point scale (1 institute)	*46*	*16.3*
Risk estimation	283	100.0
No associated risk	*209*	*73.9*
Limited-moderate risk	*65*	*23.0*
Possible risk	*9*	*3.2*
Follow-up of CAPA effectiveness**	**182**	**3.5**
Type of preventive action specified	113	62.1
Discussed with personnel (e.g. 1-on-1 or lab meeting)	*17*	*15.0*
Updated and verified the request form	*15*	*13.3*
Update and validate the final report	*14*	*12.4*
Repeated the test and verified end result	*14*	*12.4*
Additional awairness raised	*13*	*11.5*
Change or update test method, perform new validation	*10*	*8.8*
Update or change standard working procedure or personnel instructions	*8*	*7.1*
Modify and verify sample identification	*8*	*7.1*
Documented in incidents for future reference	*4*	*3.5*
Request new kit from manufacturer	*3*	*2.7*
Change integrated in laboratory information system	*2*	*1.8*
Verify correct reception of the sample	*2*	*1.8*
Involve another department	*2*	*1.8*
Unspecified	*1*	*0.9*
Date of verifying CAPA effectiveness documented	91	50.0
Same day of incident closure	*44*	*48.4*
<2 months after incident closure	*14*	*15.4*
2-4 months after incidents closure	*10*	*11.0*
>4 months after incident closure	*13*	*14.3*
30-331 days after incident opening (no closure date available)	*10*	*11.0*
A preventive action was performed, but no description or date was provided	14	7.7

*Estimated risk was only assessed by 4 of 8 institutes (see Supplemental table 1). For the institute using a 3-point scale the following risks were reported: 1=no risk, 2=limited, 3= moderate risk. For a 20-point scale: 1=no risk, 2=limited, 3-9=moderate, >10=possible risk. For the descriptive risk analyses, the risk estimation was deduced from the description given. **Laboratories could either provide a specific preventive action, or a date to verify the CAPA effectiveness, or both, which is why percentages add up to more than 100%. Abbreviations: CAPA, corrective and preventive action.