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RISK TO PATIENT SAFETY FROM LABORATORY ERRORS AND DELAYS

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DECLARATION OF AUTHORSHIP

"RISK TO PATIENT SAFETY FROM LABORATORY ERRORS AND DELAYS"

I declare that I am the author of this work, which is original. The work cites other authors and works, which are adequately referred in the text and are listed in the bibliography.

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Wei Wang

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ABSTRACT

In most of the cases, patients are diagnosed and treated directly based on the clinical laboratory results. Thus the impact of laboratory errors and delays to the patient safety is significant, and has drawn increasing attention from both the general public and the healthcare professionals. Nowadays, the laboratory error rate is still high and continuously results in serious or irreversible medical consequences. It is critical to develop an effective and efficient quality system to prevent and reduce the errors and delays, or at least detect and correct them before it is too late.

This study focuses on the risk assessment of patient safety in the entire processes (i.e. pre-analytical, analytical and post-analytical phases) in a clinical laboratory: Core Molecular Biology Laboratory (Core BM) in Hospital Cl ńic de Barcelona, which was newly-built in January 2016. It is a prospective risk assessment that helps to evaluate and improve the designed processes before their full implementation, to ensure the laboratory quality as well as patient safety ultimately.

According to ISO standards and guidelines, the processes of the Core BM were assessed using Failure Modes and Effects Analysis (FMEA), with the help of Fishbone Cause-Effect Diagram. 216 risks were identified, the majority of which were from pre-analytical and analytical phases. 21 risks were ranked as high or medium priority to be treated, which mainly focused on sample quality and manual procedures. Actions were proposed to relevant processes for implementation.

This is the first study in Europe that applied FMEA in a hospital clinical laboratory in the TTP scope, i.e. pre-analytical, analytical and post-analytical phases of Core BM. It has laid the foundation of the risk management system in the laboratory, and allows the future improvement from both detailed steps and general scope.

Keywords: Risk, Patient Safety, Clinical Laboratory, Analytical Process, FMEA

RESUMO

Na maioria dos casos, os pacientes são diagnosticados e tratados directamente com base em resultados clínicos laboratoriais. Assim, o impacto dos erros de laboratório e atrasos sobre a segurança do paciente é significativo, e tem atraído cada vez mais atenção tanto do público em geral como dos profissionais médicos. Hoje em dia, a taxa de erro de laboratório é ainda elevada e resulta continuamente em consequências médicas graves ou irreversíveis. É fundamental desenvolver um sistema de qualidade eficaz e eficiente para prevenir e reduzir os erros e atrasos, ou pelo menos detectar e corrigi-los antes que seja tarde demais.

Este estudo centra-se na avaliação de risco da segurança do paciente nos processos completos (ou seja fases pré-analítica, analítica e pós-analítica) num laboratório clínico recém-inaugurado: o laboratório de Biologia Molecular núcleo (Núcleo BM) no Hospital Clínic de Barcelona. O estudo é uma avaliação do risco potencial que ajuda a avaliar e melhorar os processos concebidos antes da sua plena aplicação, de forma a garantir a qualidade de laboratório, bem como a segurança do paciente, em última instância.

De acordo com as normas e diretrizes da ISO, os processos do núcleo BM são avaliados utilizando o método "Failure Modes and Effects Analysis" (FMEA), com a ajuda de diagramas de causa-efeito espinha de peixe. Foram identificados 216 riscos, a maioria das quais eram de pré-Analytica e fases de análise. 21 riscos foram classificados como de alto ou médio prioridade a ser tratado, que se concentrou principalmente na qualidade da amostra e procedimentos manuais. Ações foram propostas para os processos relevantes para a implementação.

Este é o primeiro estudo na Europa, que aplicado FMEA em um laboratório clínico hospitalar no âmbito TTP, isto é, as fases pré-analítica, analítica e pós-analítica do núcleo BM. Ele lançou as bases do sistema de gestão de risco em laboratório, e permite a melhoria futura de ambas as etapas detalhadas e alcance geral.

Palavras chave: Risco, Segurança do Paciente, Laboratório Clínico, Processo Analítico, FMEA

LIST OF ACRONYMS

AF	Fragment Analysis
CDB	Biomedical Diagnostic Center
CE	Extraction Center
CLI	Clinical Laboratory Interface
CLSI	Clinical and Laboratory Standards Institute
Core BM	Core Molecular Biology Laboratory
FMEA	Failure Modes and Effects Analysis
HCB	Hospital Clínic de Barcelona
ISO	International Organization for Standardization
PCR	Polymerase Chain Reaction
QC	Quality Control
Reception CE	Reception of Extraction Center
RL	Risk Level
RM	Reception of Samples (Reception de Muestras)
RPN	Risk Priority Number
SEQ	Sequencing
SIL	Laboratory Informatics System
SOP	Standard Operating Procedure
TAT	Turnaround Time
TTP	Total Testing Process
UGC	Client Management Unit (Unidad de Gestión de Clientes)
WL	Worklist

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1 INTRODUCTION

1.1 Patient Safety in Healthcare Industry

Among the 10 facts published by WHO in 2014, it is estimated that in developed countries as many as 1 in 10 patients is harmed while receiving hospital care [1]. This rate is nowhere lower in the European countries: every 10th patient in Europe experiences preventable harm or adverse events in hospital, causing suffering and loss for the patient, their families and healthcare providers, and taking a high financial toll on healthcare systems [2].

The moral imperative that generations of students and doctors have taken to be an ethical foundation to their practice – "first do no harm" – is one that is flouted inadvertently or deliberately on a daily basis [3]. However nowadays healthcare is not as safe as it should be. What goes wrong? According to the Murphy's Law, whatever can go wrong, will go wrong. In the context of healthcare industry, it works the same. And the cost is inevitably – patient safety.

Based on 1984 data developed from reviews of medical records of patients treated in New York hospitals, the US Institute of Medicine (now National Academy of Medicine) published the famous report: "To Err Is Human: Building a Safer Health System." [4], which dropped a bombshell on the healthcare industry by reporting that up to 98,000 Americans per year die directly as a result of medical errors. The number disclosed that medical errors represent one of the leading causes of death and injury in the US [5], probably the third one following heart diseases and cancers [6, 7]. The fact was reinforced the next year by the UK's "An Organisation with a Memory" [8].

Since then, the issues of patient safety and medical errors have become important topics in health policy and healthcare practice in several countries. And they are discussed ubiquitously in the mass media to continuously draw attention and criticism of the public. The healthcare professionals have been making more prospective effort to counteract this problem. The US, Australia, UK, Denmark and Canada are among the pioneers to build a safer healthcare system for patients by initiating focused efforts to reduce medical errors and improve patient safety [9].

Despite the worldwide concern of this topic, there is no standard definition of "patient safety". WHO defines "Patient safety is the absence of preventable harm to a patient during the process of healthcare. The discipline of patient safety is the coordinated efforts to

prevent harm, caused by the process of healthcare itself, from occurring to patients." [10]. Summarizing the similar definitions from the WHO Regional Office for Europe [11], the UK National Health Service (NHS) [12], the Agency for Healthcare Research and Quality [13], and academic books and literatures [14, 15], the main characteristics of "patient safety" are:

(1) The ultimate goal is to eliminate preventable harm from reaching to the patient;

(2) Preventable harm is generated during healthcare processes, which include errors that deviate from the good medical practise, and preventable accidents during the course of healthcare service (e.g. accidental falls);

(3) Preventable harm may cause physical or mental injury for a patient (from mild to severe);

(4) Errors that could have caused harm to patients should also be considered (potential hazard);

(5) The approach is to prevent, recover and reduce errors and accidents as much as possible;

(6) Ensuring patient safety is a systematic effort through the processes of delivering care in a complex system, not an "individual provider issue".

Despite the continuous effort made by healthcare professionals, the situation seems to be worse. An updated estimate was developed from modern studies published from 2008 to 2011. The number of premature deaths associated with preventable harm to patients was estimated at more than 400,000 per year in the US. Serious harm seemed to be 10- to 20-fold more common than lethal harm [16]. However, the data revealed is only a tip of an iceberg. First, the data is only about deaths, not including other level s of harms. Second, the outpatient data is difficult to collect. Third, the studies can only collect the incidents that are directly attributed to healthcare process while many lay hide due to lack of clear evidence. Fourth, the data is not adequately reported largely as a result of attempting to avoid blame. In the UK, it is estimated that only 5% of incidents are adequately reported [17].

While healthcare has become more effective it has also become more complex, with greater use of new technologies, medicines and treatments [11]. Admitting the fact that the automation, modern technology and better trained staff may have reduced the possibility of

errors, patient harm caused by medical errors increased nonetheless. The reasons could be complex:

- Increased complexity of medical practice and operational management
- Higher expectation vs. more difficult decisions required by aging population and complicated diseases
- Overloaded work with rapider patient flow vs. increasing economic pressure
- Overuse of risky, invasive, revenue-generating procedures
- Over-confidence on new technology and procedures
- Barriers in cross-disciplinary teams communication

Patient safety is a multifactorial and complex issue that has no one-shot solution. It needs all parties' effort and cooperation. These efforts rely on the patient and his family, the healthcare professionals and organizations, in the regulatory and accreditation bodies, among suppliers, and at policy levels, including government and non-governmental organizations.

Patient safety is now recognized in many countries, with global awareness fostered by the WHO's World Alliance for Patient Safety. And yet there continue to be significant challenges to implementing patient safety policies and practices. However it is worthy of accepting these challenges not only for the patient welfare, but also for saving the resources and costs for the healthcare industry and the government. European Statistics show that strategies to reduce the rate of adverse events in the European Union alone would lead to the prevention of more than 750,000 harm-inflicting medical errors per year, leading in turn to over 3.2 million fewer days of hospitalization, 260,000 fewer incidents of permanent disability, and 95,000 fewer deaths per year [2].

1.2 Clinical Laboratory and Patient Safety

Diagnostic errors are an important source of preventable harm [18]. To a large extent, the diagnosis for patients depends directly on the clinical laboratory results [19, 20]. Laboratory testing is widely used to diagnose disease and disease subtypes, to determine optimum treatments and patient's likely response to a treatment, to make judgment of patient's recovery, etc. Among medical errors, the laboratory errors are the mostly neglected,

underestimated, but significant factor which contributes almost 55-58% of diagnostic errors [20, 21].

Therefore, it is very important to make sure that laboratory services are of high quality – as medical decisions made based on them could only be as good as the quality of the results supplied. To better control the quality delivered by the clinical laboratory, generations of physicians tried to describe the loop of testing process. Thus, a now widely accepted concept of "Total Testing Process" (TTP) evolved through the past 40 years.

The concept was firstly shaped in 1971 aiming to aid the predicted automated clinical laboratory testing process [22]. Lundberg developed the idea to the "brain-to-brain turnaround time loop", focusing more on the patient-clinician reaction and the interaction with the laboratory test. "A laboratory test begins when a clinician's brain decides there is a need for such a test. It proceeds through a series of steps from that point forward: Question, test selection, ordering, identification of patient and specimen, collection, transportation, preparation, analysis, reporting, interpretation, and action." [23]. Sometimes the first two steps are integrated to the ordering step since they are in the brain of the clinician that will be reflected in the ordering. Schumacher, *et al*. suggested "patient effect follow-up" should be added after action as the final step [24].

The TTP is a systems-based framework for the evaluation of the interactions, connections, and activities involved in the testing process. The process is circular and includes the all phases of the testing cycle. Cognitive tasks are required at multiple steps, by both the primary care provider and the laboratory [25]. Anything that stands in the way of the prompt and perfect receiving of laboratory results for the patients is perceived as a "laboratory problem or error." If any inappropriate action occurs within this loop, it will cause, at the most, a tragedy and, at the least, a waste [26]. This framework allows the design and implementation of interventions that may reduce or eliminate errors that adversely affect testing and patient-health outcomes. This framework also allows for the study of barriers and limits to quality-improvement activities. The TTP encompasses all components or steps of the cycle from the point of the clinical question to the point of clinical action [25]. Traditionally it is a cycle consisting of three phases: pre-analytic, analytic, and post-analytic phases. Figure 1 shows the TTP adapted from Smith, *et al*. [25] and Plebani, *et al*. [27].

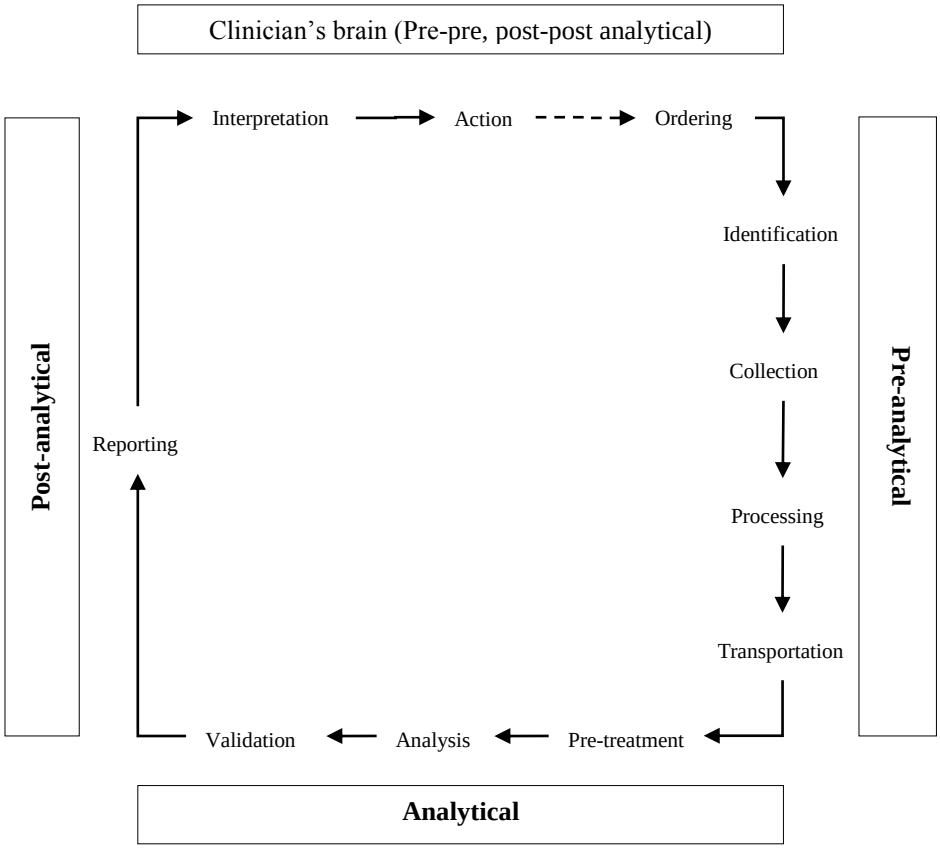

Figure 1. The Brain-to-Brain Loop of TTP (adapted from [25, 27])

The quality of all processes occurring in these phases, associated in a workflow, determine the quality of test or results, e.g. accuracy, precision, reliability, turn-around time, etc. However, most attention - developmental and strengthening efforts (e.g. quality assurance system, new technology, maintenance etc.) - has been focused on the analytic phase. The pre-analytic and post-analytic phases, which are also referred to as clinic-laboratory interface (CLI), have been largely neglected. Errors are known to occur in any of the phases, with majority of the errors being found to occur in the pre-analytic and post-analytic phases. The testing processes that are more affected are those that occur outside the laboratory, meaning at healthcare facilities. Such processes include: specimen collection, storage of specimen, specimen packaging and transportation, completion of test forms, test ordering, test result collection and filing, and finally using and acting upon the results for patient management and decision making. Some of the errors particular to CLI include inappropriate test requests, misidentification of patient, inappropriate test tube, inadequate sample collection and transport, inadequate sample/anticoagulant volume ratio, insufficient sample, labelling errors, improper data entry, etc. For the provision of high quality laboratory services that respond to healthcare needs, it would be necessary to pay attention

and strengthen all the phases in laboratory process cycle [28]. With this consideration, this study includes all the upstream and downstream workflow of Core BM to assess the risk.

1.3 Clinical Laboratory Quality Management

The past decades have seen sustained improvements in analytical performances, such as the reduction of the turnaround time (TAT), but the error rate, particularly in pre- and post-analytical phases is still high [29]. There exist many obstacles to build a clear and quantity-oriented monitoring system. The lack of a universally accepted methodology and "allowable error rate", the practical difficulty in reporting and measuring the number of errors, reduce the possibility of evaluating the impact of laboratory errors on patient safety. Bonini, *et al*. pointed out several major factors: there is a need for better definition of laboratory errors and their causes, for classifying laboratory errors by relating them to their effects on patient outcomes, and for allowing definition of the relevance of the error itself. A standard for laboratory error detection and reporting needs to be defined, and an accurate analysis of the risk of errors in the clinical laboratory needs to be performed.

Among recent independent studies, laboratory error data was collected from worldwide healthcare organizations and analyzed. Different error classification systems and safety assessment criteria were proposed. Specific risk management guidelines were also developed for managing the health risk in clinical laboratory errors [30, 31]. Risk management can minimize the chance of errors and ensure reliability of test results in a prospective way. It develops various quality control activities employed by the laboratory to achieve the goal of generating accurate and reliable test results.

1.4 Risk Management and Patient Safety

Compared to the risks in any other industries, healthcare is a relatively high risk area [32] and has less tolerability of errors. Medical errors are extremely serious and thus very sensitive to the general public.

ISO/IEC Guide 51:2014 defines "safety" as "freedom from risk which is not tolerable" [33]. "ISO15189:2012 Medical laboratories - Requirements for quality and competence" requires: "The laboratory shall evaluate the impact of work processes and potential failures on examination results as they affect patient safety, and shall modify processes to reduce or eliminate the identified risks and document decisions and actions taken." [34]. To ensure patient safety, as a part of clinical laboratory quality management system, risk management

for a clinical laboratory is a necessity. It is a valuable tool that can help managers and clinical staff improve their work and the care delivered to patient [35].

Risk management benefits the healthcare industry as it:

- Strives for the optimal balance of risk by focusing on the reduction or mitigation of risk while supporting and fostering innovation so the greatest returns can be achieved with acceptable results, costs and risks;
- Helps healthcare organizations comply with the quality standards and obtain or maintain accreditations;
- Supports better decision-making through a solid understanding of all risks and their likely impact;
- Helps healthcare organizations plan for uncertainty, cope with the impact of unexpected events and increase staff, patient and public confidence in care that is delivered with well-considered contingency plans;
- Highlights the weakness and vulnerability in procedures, practices and policy changes.

2 STUDY OBJECTIVES

This risk assessment study is designed to identify and assess the potential risks that could affect patient safety in the Molecular Biology Laboratory (Core BM) and related pre-analytical and post-analytical areas; to propose improvement actions in order to remove, reduce or control the risks; and to lay the foundation of the risk management system for Core BM.

3 RATIONALE AND METHODOLOGIES

According to the ISO31000 [36], the process of risk management is shown in Figure 2.

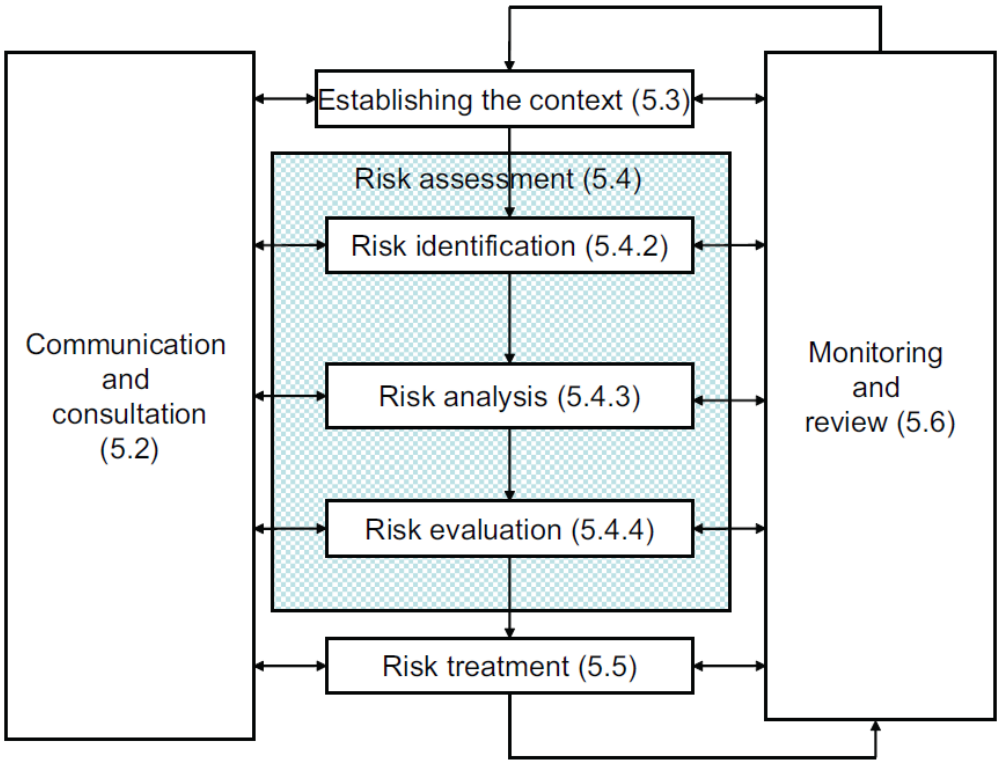

Figure 2. Risk Management Process [36]

Ideally, risk assessment is performed at the start of a new system design or before its implementation. For ongoing systems, a retrospective risk assessment can also be performed to make improvements. However, considering the organizational structure and heavy workload in the reality of Core BM, the risk assessment is performed in different situations:

(1) For pre-analytical and post-analytical phases, both are functioning according to a well-established system. Only the interface processes with Core BM are new. However all of the processes have impact on the Core BM work flow, and they have never been assessed this way. A risk assessment was performed for all the processes in pre-analytical and post-analytical phases, also considering that almost 80% of laboratory errors originate from these less-automated areas [20].

(2) For the analytical phase, since the Core BM clusters several common functions within the CDB, all the working processes are maintained directly from previous functions and are implemented immediately. The risk assessment can only be performed while the system is functioning. What makes the situation more complicated is: new equipments are under testing while the old equipments are still in service; all the equipments are functioning while being adjusted frequently; the interfaces with other services are new and not unified.

Considering the time limitation, the step of risk treatment, monitoring and review were not performed within this study but will be continued in the hospital.

3.1 ISO Standards of Quality and Risk Management

The laboratory follows the general principles of "ISO15189:2012 Medical laboratories — Requirements for quality and competence" [34]. This study follows "ISO31000:2009 Risk management" [36], and "ISO/IEC Guide51:2014, Safety aspects — Guidelines for their inclusion in standards" [33]. The terminology used in this study refers to "ISO/IEC Guide73:2009 Risk management – Vocabulary - Guidelines for use in standards" [37].

3.2 Failure Modes and Effects Analysis

While the whole system related to Core BM is functioning without previous risk assessment, a prospective Failure Modes and Effects Analysis (FMEA) is performed. Ideally, FMEA begins during the earliest conceptual stages of design and continues throughout the life of the system service when changes occur. In the case of Core BM, FMEA was performed at the time of transition and trial operation.

From the ISO/TS22367[1] definition, FMEA is a systematic review of a system or product involving identification of potential failures and assessing the impact on total system/product performance of that failure. FMEA was first introduced in US military in 1960s and developed by the aerospace and automotive industries [38]. It has been adopted by the healthcare industry since 1990s. With the requirement of JCHAO [39], now FMEA is universally applied in healthcare industry especially in clinical laboratory [40]. This study adopts the Clinical and Laboratory Standards Institute (CLSI) guidelines for FMEA [30] and customizes the methodology according to the actual situation for Core BM.

The steps applied in this study are as follows (adapted from the recommendation of American Society for Quality [38]:

1) Assemble a cross-functional team of people with diverse knowledge about the organization, process, equipments and customer needs.
2) Identify the scope and boundaries of the FMEA. It is for the newly-built Core BM and all its related processes. It should be as detail as possible to identify every possible error.

[1] ISO/TS 22367: 2008. Medical laboratories—reduction of error through risk management and continual improvement

3) Break the scope into separate subsystems: pre-analytical, analytical and post-analytical phases. Within each subsystem, identify different processes dedicated to diverse functions.

4) For each function, identify all the potential failure modes for every process (how the process could go wrong), with the help of process maps. This is a brainstorming step that needs to analyze all the factors within each single process and to hypothesize the ways they can go wrong.

5) For each failure mode, identify all the potential consequences on the process, related processes, or the delivered outcome (identify all possible "Immediate Effects" in regards of process failure or testing result), and finally on patient safety ("End Effects"). Determine how serious the "End Effects" is. Severity (S) is rated on a scale from 1 to 5 (Table 1). If a failure mode has more than one potential "End Effects", use the highest severity score (the worst).

Table 1. Severity Scoring Criteria

Severity (S)	**The potential end effects on lab result output for one run, or directly on patient safety**	
Value	**Significance**	**Definition**
1	No relevant effect on safety	No effect on patient safety, system operable, history data not well maintained
2	Minor	Result acceptable with minor defect or can be corrected easily and immediately, patient mental discomfort (confusion, anxiety, distrust, etc.)
3	Moderate	Result acceptable with obvious defect, need more effort to correct. E.g. inaccurate or incomplete
4	Critical	Delayed or unreliable result, unacceptable result or repetition needed, delayed diagnosis/ treatment, patient is mal-treated physically, e.g. blood is taken more than necessary
5	Catastrophic	Erroneous result that will misleading the diagnosis, no result, or patient safety is directly jeopardized. E.g. incorrect or reversed result, patient is treated with wrong approach or adverse event is resulted

6) For each failure mode, determine all the potential causes applying the best knowledge and experience of the team. The causes are used to estimate the probability (P), to identify the existing detection methods for assigning detectability (D), and finally to propose actions.

7) For each failure mode, determine the probability of its occurrence during the lifetime of the scope (considering all the causes that could result in this failure mode). Determine

how likely or frequently it is to occur. Probability (P) is rated on a scale from 1 to 5 (Table 2). The probability can be estimated with the reference of the relevant history record, if exists.

Table 2. Probability Scoring Criteria

Probability (P)	Frequency or likelihood to which extent the failure mode is likely to occur	
Value	**Significance**	**Definition**
1	Extremely unlikely or Never detected	< 1 in 150,000 patients or cases (< 0.0007%)
2	Remote	> 1 in 10,000 patients or cases (0.01%)
3	Occasional	> 1 in 2,000 patients or cases (0.05%)
4	Reasonably possible	> 1 in 200 patients or cases (0.5%)
5	Frequent	> 1 in 20 patients or cases (> 5%)

8) For each failure mode, identify current methods of detection for all the causes and the failure mode itself. These methods might prevent the causes from leading to a failure, reduce the probability of occurrence or detect the failure mode after its occurrence but before the patient safety is affected. In other words, the detectability defines the probability of stopping the failure from leading to the end effect on patient safety. The score determines how difficult it is to detect the failure mode or its causes. Detectability (D) is rated on a scale from 1 to 5 (Table 3).

Table 3. Detectability Scoring Criteria

Detectability (D)	The possibility of detecting either the failure mode or its cause(s) using current existing methods after their occurrence and before the patient safety is affected	
Value	**Significance**	**Definition**
1	Certain - always detectable	Current methods are almost certain to detect. Reliable detection controls are known with clear process
2	High	High likelihood current methods will detect
3	Moderate	Moderate likelihood current methods will detect
4	Low	Low or remote likelihood current methods will detect
5	Undetectable - impossible to detect	No known methods are effective to detect

9) Organize team review meetings to review the identified failure modes, effects, causes, detection methods, and the rating is given with the agreement of all team members. This is a time-consuming step that needs rounds of discussions to reach final agreement.

10) Calculate the risk priority number (RPN), which equals S × P × D. These numbers provide guidance for ranking potential failures in the order they should be treated. The RPN matrix (Table 4) defines the priority of treating the risks.

Table 4. RPN Matrix

RPN		RL													
		1	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**10**	**12**	**15**	**16**	**20**	**25**
Detectability	**1**	1	2	3	4	5	6	7	8	10	12	15	16	20	25
	2	2	4	6	8	10	12	16	18	20	24	30	32	40	50
	3	3	6	9	12	15	18	24	27	30	36	45	48	60	75
	4	4	8	12	16	20	24	32	36	40	48	60	64	80	100
	5	5	10	15	20	25	30	40	45	50	60	75	80	100	125

RPN
Low
Minor
Medium
High

11) Propose recommended actions. These actions may be design or process changes to lower severity or probability. They may be additional methods to improve detection.

12) As actions are completed, evaluate new S, P or D ratings and calculate new RPNs. Check if improvements are shown after the implementation of the recommended actions.

13) Note: Risk in FMEA is identified by "failure mode". Each "failure mode" can result in multiple effects and can have multiple causes. As such, finally multiple actions can be proposed to all the causes to eliminate the occurrence of one "failure mode" (one row).

3.3 Fishbone Cause-Effect Diagram

The fishbone diagram (Ishikawa Diagram) helps to structure a systematic thinking. It identifies all the possible cause categories for a general effect (the loss of a function) and helps in FMEA step 6. This study developed the fishbone diagrams with the reference of American Society for Quality [41]. They are described for for pre-analytical phase (Figure 3) analytical phase (Figure 4) and post-analytical phase (Figure 5).

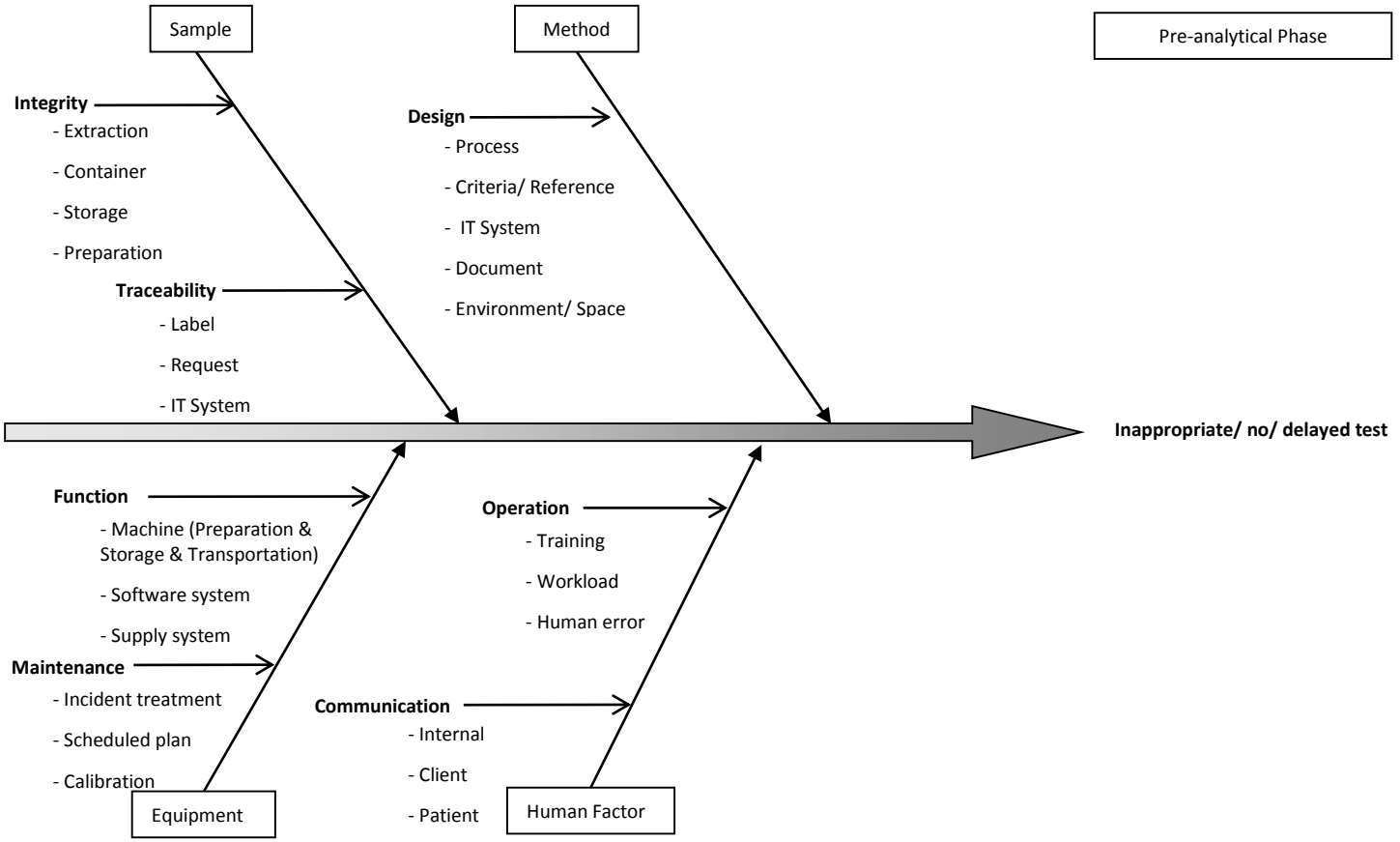

Figure 3. Fishbone Diagram for Errors or Delays in the Pre-analytical Phase

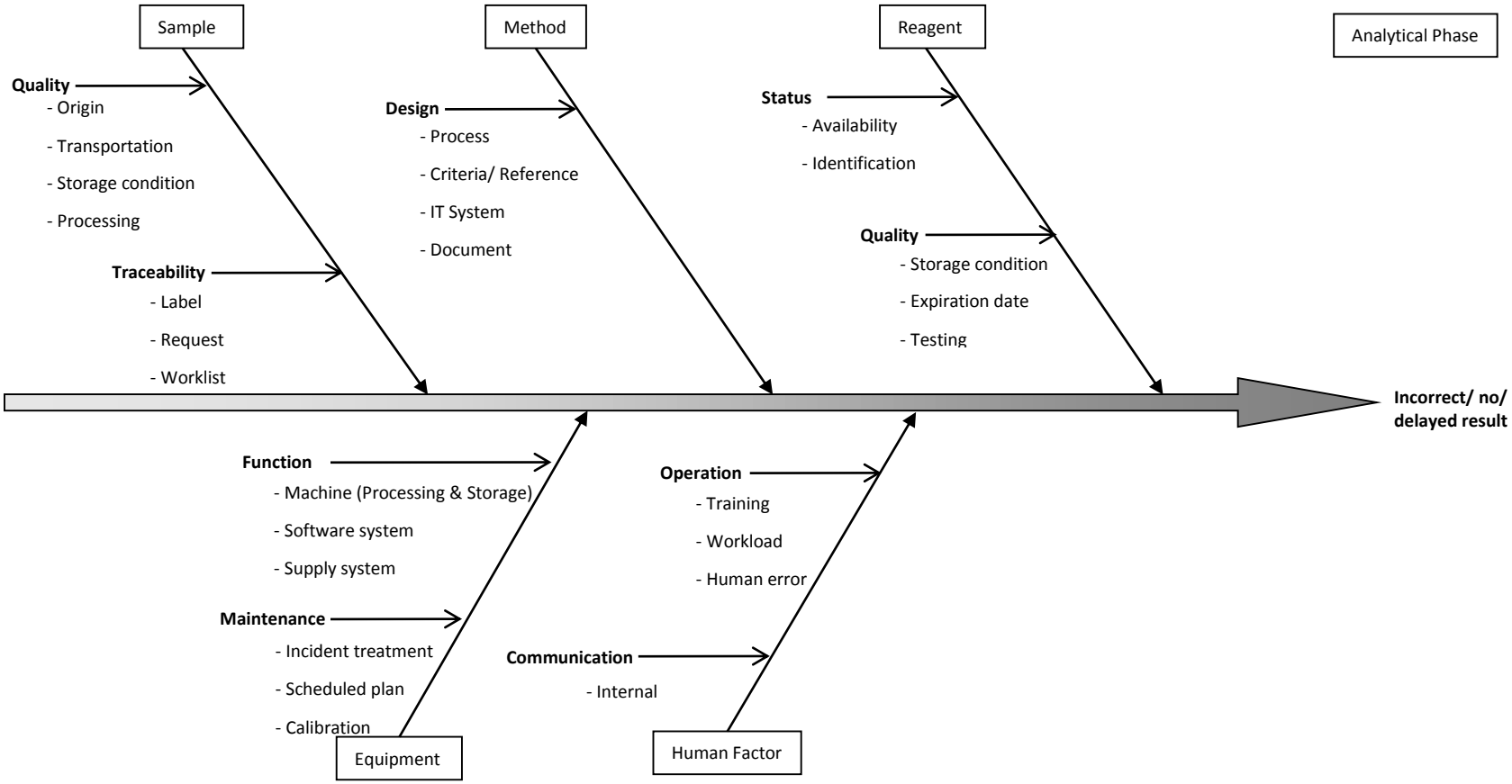

Figure 4. Fishbone Diagram for Errors or Delays in the Analytical Phase

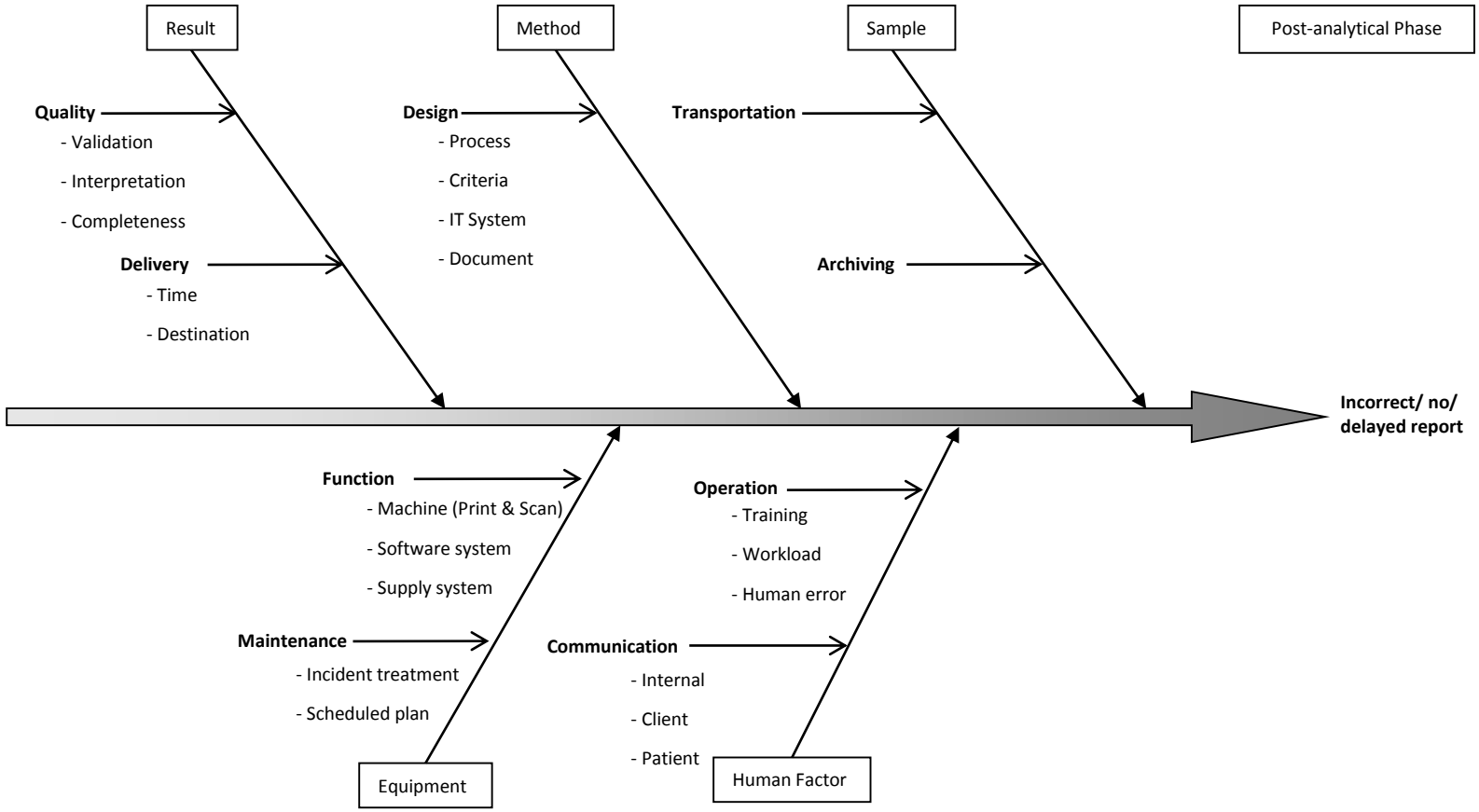

Figure 5. Fishbone Diagram for Errors or Delays in the Post-analytical Phase

4 RESULTS AND DISCUSSIONS

4.1 Scope and Boundaries

This study was applied to the Core BM in the Biomedical Diagnostic Center (CDB) of Hospital Cl ńic de Barcelona. The Core BM was newly-built in January 2016 to centralize a series of DNA analysis services that were previously performed separately by individual department.

The CDB comprises all the laboratories of Hospital Cl ńic de Barcelona. It attends to the laboratory needs of 400,000 patients annually from Hospital Cl ńic de Barcelona and receives samples from 80,000 patients seen in other hospital centers and private laboratories. Approximately 7,000,000 determinations within 2,327 different tests are performed per year [42].

To assess the risks, the entire workflow of the Core BM was studied, including pre-analytical, analytical and post-analytical phases. The CDB laboratory departments studied are described in the organization chart in Figure 6.

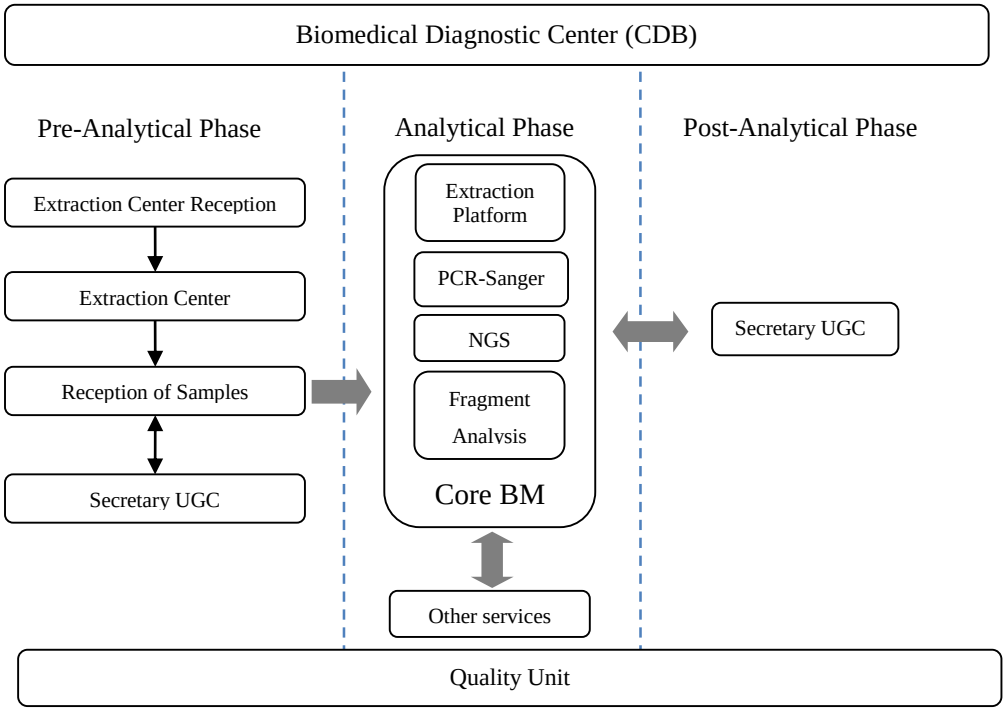

Figure 6. CDB Organizational Chart

General function of each department:

- Extraction Center Reception (Reception CE): Patient goes to the Reception CE first to activate the test request(s) and/or to ask for information. The detailed processes are shown in Figure 7.
- Extraction Center (CE): Patient blood sample is extracted and urine sample is collected in CE. The detailed processes are shown in Figure 8 and Figure 9.
- Reception of Samples (RM): The internal and external samples are received, registered, processed and transported to analytical laboratories. The detailed processes and its interaction with Secretary UGC are shown in Figure 10.
- Secretary UGC: For both pre-analytical and post-analytical phases, the internal and external incidences and requirements are managed, documents and result reports are archived and managed. The detailed processes are shown in Figure 11 and Figure 12.
- Core BM Extraction Platform: Samples from RM and other internal and external clients are received, registered. DNA is extracted, normalized and quantified. The detailed processes are shown in Figure 13 and Figure 14.
- Core BM PCR Sanger: From the extracted DNA, the entire PCR Sanger sequencing process is performed. The entire processes are shown in Figure 15, Figure 16 and Figure 17.
- Core BM NGS: Currently NGS robot process has not been established. This study excludes the NGS process.
- Core BM Fragment Analysis: It is performed for the DNA samples sent from other services. The detailed processes are shown in Figure 17.
- Other services: Samples of different type can be sent directly from other CDB services to Core BM, and are extracted or analysed here. In some cases samples are returned to these services per request. The interaction between Core BM and other services are generally shown in Figure 13 and Figure 17.

4.2 Cross-Functional Team Organization

The professionals included in the cross-functional team are:

Pre- and Post-analytical area team: 2 laboratory coordinators, 1 quality unit expert, 1 facilitator;

Analytical area (Core BM) team: 2 technicians, 3 laboratory physicians (one of them is also the Core BM manager, and another one is the Core BM quality manager), 1 quality unit expert, 1 facilitator.

3 rounds of review meetings were held for reviewing and assessing the risks of pre- and post-analytical area; while 6 were held for reviewing and assessing the risks of Core BM.

4.3 Process Maps

In this chapter, the process maps for each individual department are described in detail (Figure 7 to Figure 17), based on the observational studies and interview with 4 staff in Reception CE, 8 staff in CE, 12 staff in RM, 7 staff in Secretary UGC, 7 technicians and 3 physicians in Core BM.

General instructions of reading the process maps:

- Following each process map, a detailed annotation is described for each numbered step. The same steps across the departments are not described repeatedly.
- The dash lined steps are performed by other departments, which interact with the department described in the process map.
- The multi-process steps are either described in a separate process map, or described in the following text.

4.3.1 Pre-analytical Phase: Reception of Extraction Center

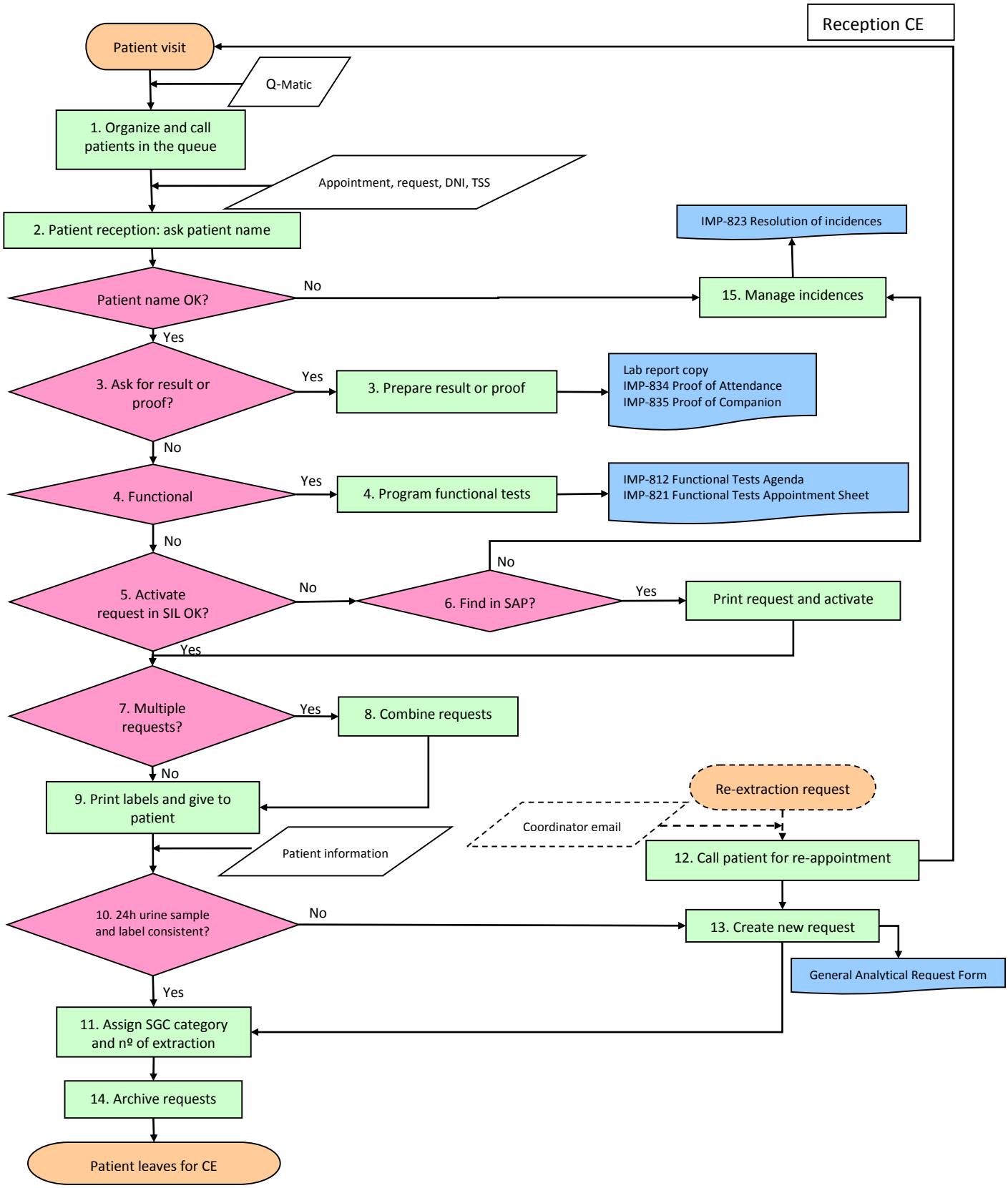

Figure 7. Process Map of Reception CE

1. Organize and call patients in the queue: Patients are grouped according to the appointment time (every 15 min is one group). Q-Matic displays the current appointment group on the screen. Patients who have the appointment of this time queue in front of the reception desks and go to the desks one by one. After the completion of one group (about 15 min), call the next group by pressing the Q-Matic keyboard.

2. Patient reception: ask patient name: ask the name of the patient, check the consistency with the lab test request that the patient brings. If the patient does not bring the request, check with the other documents that the patient brings: appointment, DNI (ID card) or TSS (Social Health Card).

3. Ask result or proof? : If the patient comes to fetch his previous test result, print a lab report copy as requested. If the patient asks for a proof of attendance or a proof of companion, prepare accordingly and stamp it.

4. Functional tests? : If the patient comes to schedule his functional tests, desk 4 staff should program the schedule in the excel "IMP-812 Functional Tests Agenda" and manually complete the "IMP-821 Functional Tests Appointment Sheet" and give to the patient.

5. Activate request in SIL OK? : If the patient comes with a request to give samples, activate the request in SIL by scanning the barcode of request number. Manage incidence if it occurs.

6. Find in SAP? : When the patient does not bring his request or request cannot be activated in SIL, search in SAP to find the correct request.

7. Multiple requests? : Patient may come with more than one request. There are different tests on different requests.

8. Combine requests: Activate each request and select "combine" in SIL. SIL automatically adopts the number of the oldest request. By doing so, all the tests have the same request number.

9. Print labels and give to patient: After the activation of all requests for one patient, print all the test labels and give them to the patient.

10. 24h urine sample and label consistent? : When there is a label for "24h urine", if the patient does not bring the sample, create a new request for the test "24h urine" in SIL so

that the patient can bring the sample next time. If patient brings the sample or there is no label for “24h urine”, patient can leave for extraction directly.

11. Assign SGC category and n ºof extraction: According to the information given by the patient himself or from the request, assign SGC category (Normal, Urgent, Port-a-cath, Sintrom, Wheelchair, Histocompatibility, Myelography) and n ºof extraction and give the ticket to the patient.

12. Call patient for re-appointment: If a re-extraction request email from the coordinator is received, call the patient and make a new appointment for extraction. The email contains all information such as patient name, old request number, test name, reason for re-extraction, etc.

13. Create new request: Register in SIL the repeated tests and complete manually “General Analytical Request Form”, only for the “24h urine” and other repeated tests. In the case of “24h urine” (patient is present without 24h urine sample), patient should bring the new request form together with the sample in his next visit. In the case of phone call re-extraction, archive the new request form and activate when patient comes for re-extraction.

14. Archive requests: When patient leaves for extraction, archive the requests activated. In the case of phone call re-extraction, archive the printed email together with the manual request form for patient’s next visit.

15. Manage incidences: Try to solve the incidence immediately. When nonconformity occurs, register in “IMP-823 Resolution of incidences”.

4.3.2 Pre-analytical Phase: Extraction Center

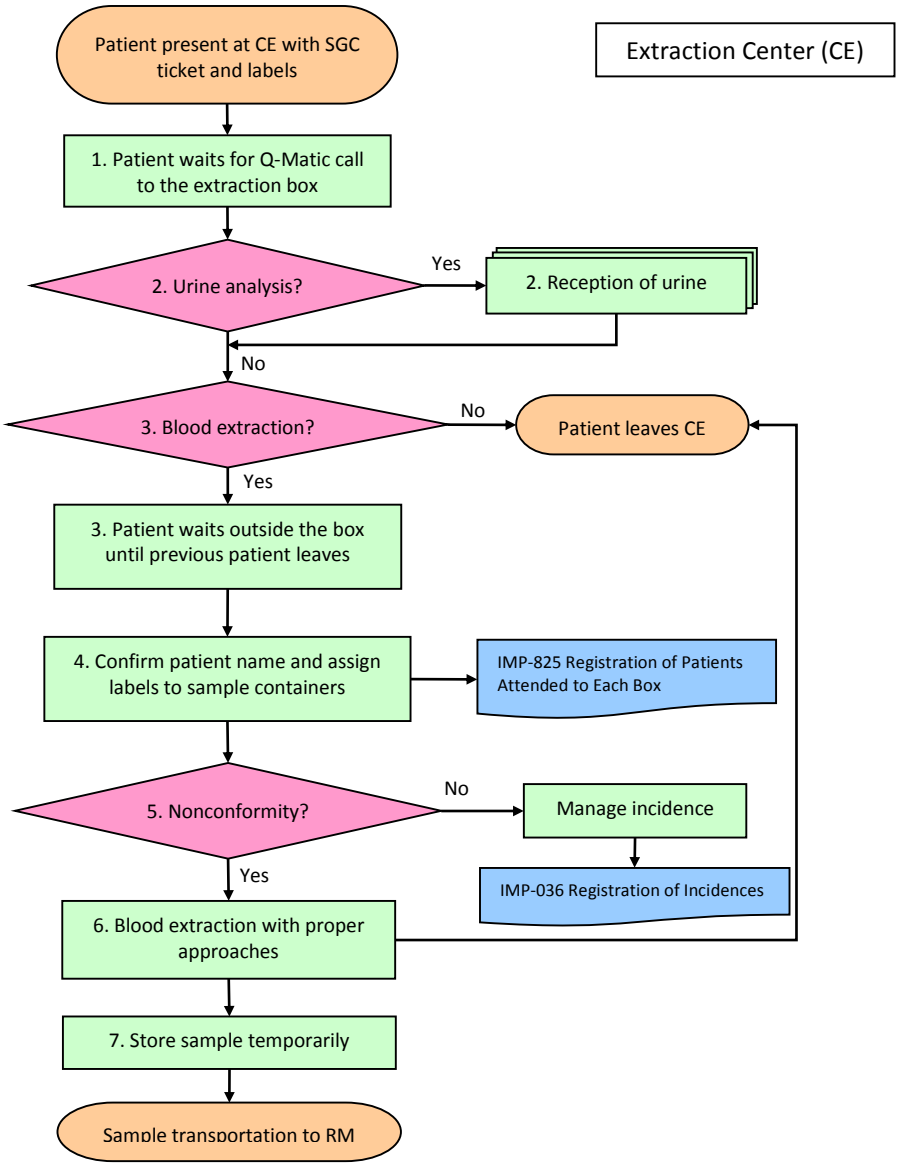

Figure 8. Process Map of CE

1. Patient waits for Q-Matic call to the extraction box: Patient comes to CE with SGC ticket and labels (and sometimes with 24h urine sample), waits until his number appears on the Q-Matic screen.

2. Urine analysis? : If there is urine sample(s) to be collected, patient stops firstly at the urine reception desk and follows the processes of "Reception of Urine" (Figure 9). If no urine sample, patient goes to the assigned box for blood extraction.

3. Blood extraction? : If no blood sample is going to be collected, patient can leave the CE. Otherwise patient should wait outside the assigned box until the previous patient leaves.

4. Confirm patient name and assign labels to sample containers: Extractor asks the patient name and checks with the name on the label(s). The header label is pasted on “IMP-825 Registration of Patients Attended to Each Box”, and then the sample labels are assigned to corresponding types of containers (tube, syringe, etc.).

5. Nonconformity? : If nonconformity occurs, extractor should manage accordingly. Ask help from coordinator if necessary, register in “IMP-036 Registration of Incidences”.

6. Blood extraction with proper approaches: Extractor selects proper materials and approaches to extract blood samples.

7. Store sample temporarily: Extractor places the samples under required conditions (special conditions include 37℃ incubating, in ice water, light-protected container, etc.) until RM staff collects them.

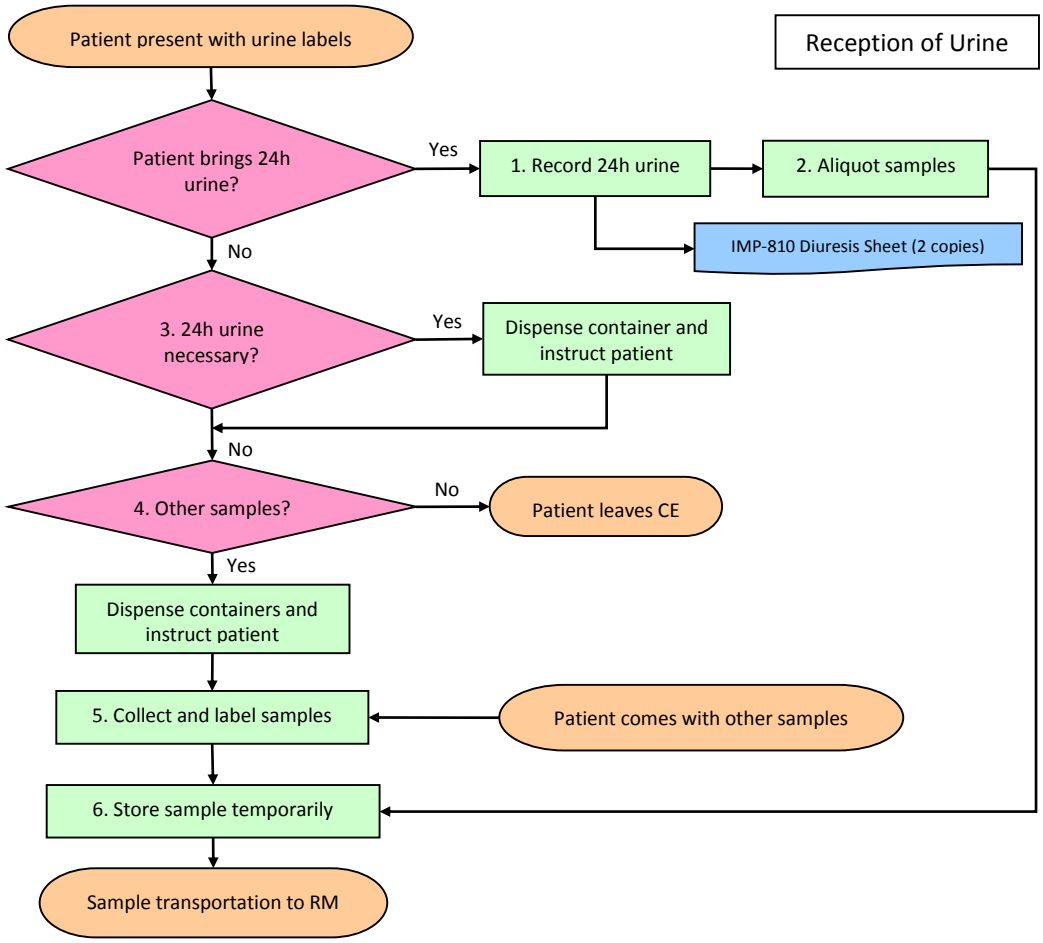

Figure 9. Process Map of CE (Reception of Urine)

1. Record 24h urine: If the patient brings 24h urine sample, weigh and record the volume (according to the weight) on two copies of "IMP-810 Diuresis Sheet".

2. Aliquot samples: Take necessary aliquot(s) as indicated by the number of label(s). If a patient has more than one bottle of 24h urine, mix before aliquoting.

3. 24h urine necessary? : If patient comes to get a bottle of 24h urine, dispense appropriate container (with or without additives) according to the test. If patient is uncomfortable to return a bottle, give 3 tubes and instruct the patient to record 24h urine volume at home.

4. Other samples? : If other samples are requested (e.g. random urine sample, sputum, feces, etc.), dispense corresponding containers and instruct patient to collect these samples and return them.

5. Collect and label samples: Collect samples returned by the patient, check nonconformity and manage incidences. Assign correct labels to the corresponding containers.

6. Store sample temporarily: Place the samples in the rack until the RM staff collects them.

4.3.3 Pre-analytical Phase: Reception of Samples

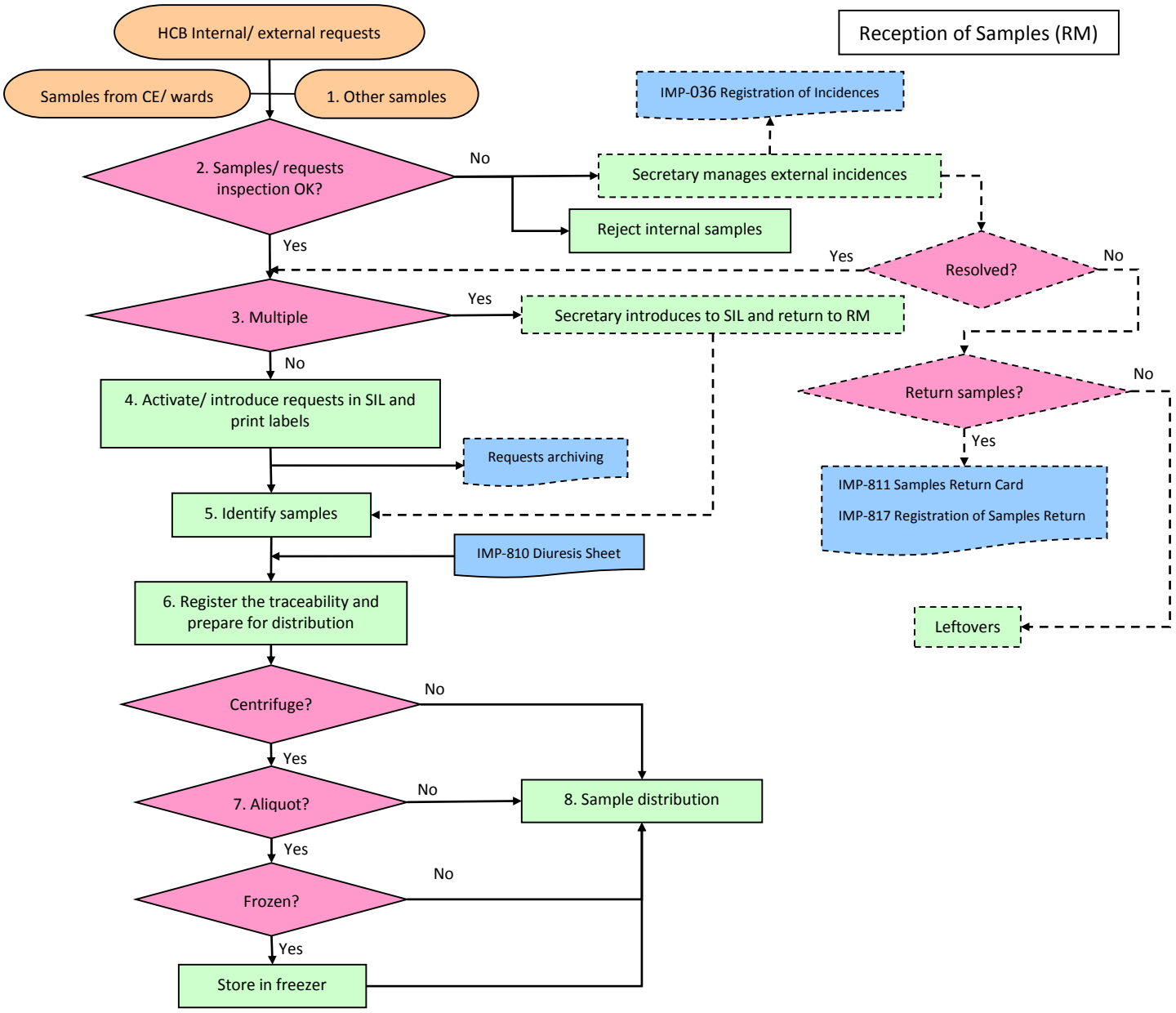

Figure 10. Process Map of RM

1. Other samples: Samples from external clients or other HCB services such as IBC, MIC, AP, etc.

2. Samples/ requests inspection OK? : Check the number of samples, sample integrity and status against the requests. If not ok, reject internal samples or send external samples to Secretary for incidence management and registration.

3. Multiple requests? : If multiple requests (>3) come in a batch, send to Secretary for SIL introduction. Keep the samples in pending boxes and wait for the labels from Secretary.

4. Activate/ introduce requests in SIL and print labels: Activate the requests in SIL by scanning request barcode. For non-standard external requests, introduce all the information manually (client, patient and test information). Print labels for all the samples. Archive the requests in different categories and send to UGC.

5. Identify samples: Match and paste the labels with the corresponding sample containers.

6. Register the traceability and prepare for distribution: For the samples transported from CE, scan for "entry" and "exit" in separate computers. For samples received at the reception desks (from the internal wards, services or external clients), scan for "exit" only. Distribute the samples according to first destinations depending on the destination code on the labels: stay for pretreatment (centrifuge, aliquot), send directly to services, send to core lab chain, etc. Register diuresis result ("IMP-810 Diuresis Sheet" received from Urine Reception) in SIL in a separate computer.

7. Aliquot? : Some blood or urine samples need multiple aliquots for different tests. Urine samples are aliquoted manually; blood samples are normally aliquoted by robot that is connected to SIL and assigns labels to aliquots automatically. For insufficient blood samples, technicians do manual aliquoting and assign labels manually.

8. Sample distribution: According to the scheduled timetable and by batch, send the samples to services for testing via different pathways. E.g. samples for MIC, IMM should be sent by pneumatic pipe; samples for IBC or external labs are fetched by particular express companies; some samples must be sent by staff manually. During transportation, the required storage condition should be respected.

4.3.4 Pre-analytical and Post-analytical Phase: Secretary UGC

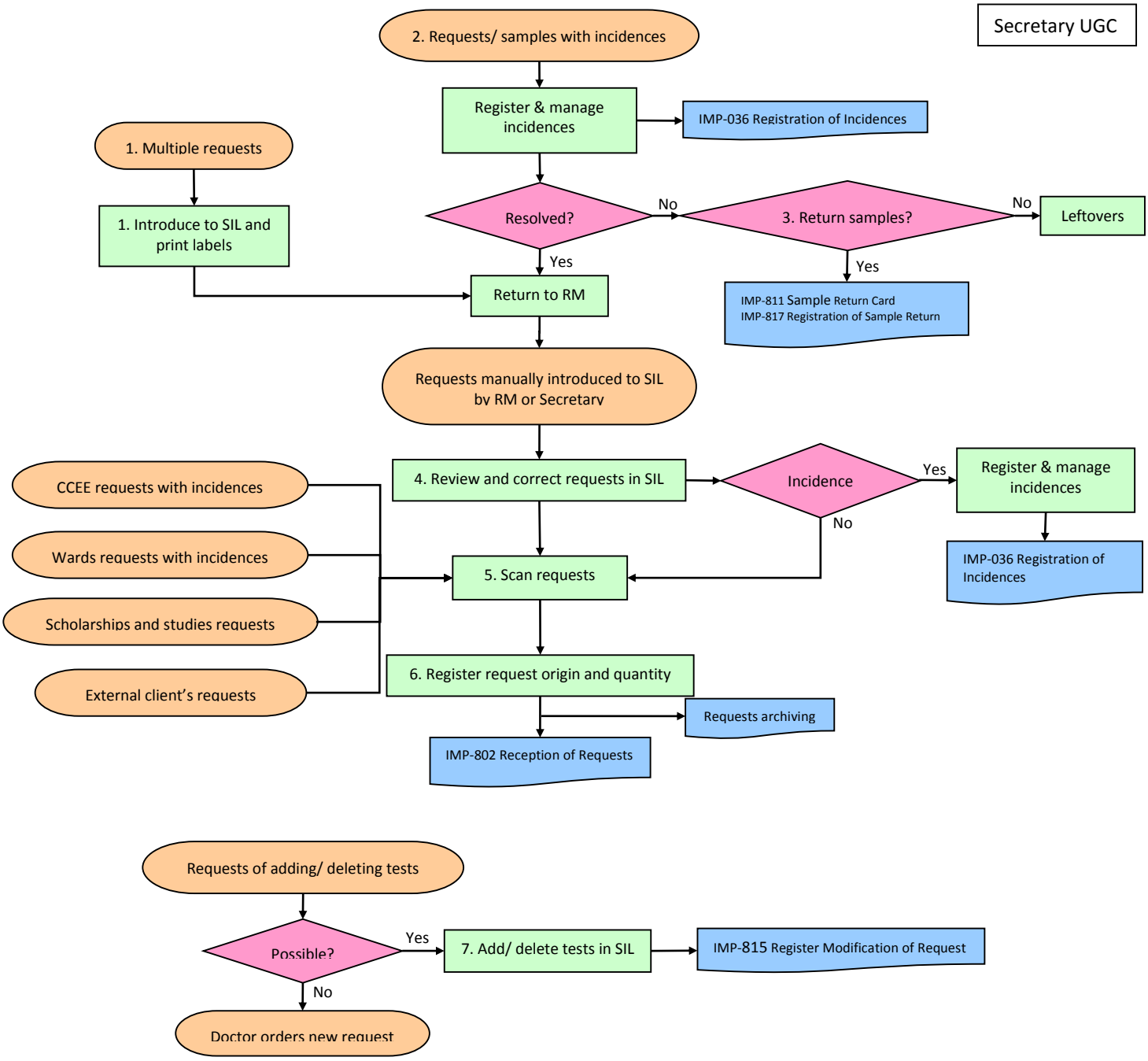

Figure 11. Process Map of Secretary UGC (Pre-analytical Phase)

1. Multiple requests: When RM receives more than 3 requests from one origin, RM keeps the samples in pending boxes and leaves the requests for secretary to introduce to SIL. Secretary returns labels to RM.

2. Requests/ samples with incidences: When there are incidences for any request or sample that RM receives, RM leaves the sample and request for secretary management. Secretary

manages and registers incidences in “IMP-036 Registration of Incidences”, and returns to RM after incidence is solved.

3. Return samples? : In case of incidence is not solved, ask client if sample(s) should be returned. If yes, prepare transportation documents “IMP-811 Sample Return Card” and “IMP-817 Registration of Sample Return”. If not, destroy the samples.

4. Review and correct requests in SIL: All the requests manually introduced by RM or Secretary should be reviewed another time. Check all the information on the original requests against the introduced information in SIL, correct errors once detected.

5. Scan requests: All the requests received should be scanned and uploaded to SIL. Check if the automatic reading of the request number is correct. If not, correct manually. Once the request number is correctly identified, the scanned file is uploaded to corresponding SIL request automatically.

6. Register request origin and quantity: At the end of the day, record in “IMP-802 Reception of Requests” the number of requests received daily according to the origin (e.g. external clients, wards, scholarships and studies, etc.). Archive the requests.

7. Add/ delete tests in SIL: Doctor calls Secretary to add or delete tests for the samples that are already in processing in the lab. Secretary checks the possibility of adding or deleting, and then accept or reject the request. The newly added test is registered directly in SIL under the ongoing samples and also on a paper form “IMP-815 Register Modification of Request”.

1. Multiple requests: When RM receives more than 3 requests from one origin, RM keeps the samples in pending boxes and leaves the requests for secretary to introduce to SIL. Secretary returns labels to RM.

2. Requests/ samples with incidences: When there are incidences for any request or sample that RM receives, RM leaves the sample and request for secretary management. Secretary manages and registers incidences in “IMP-036 Registration of Incidences”, and returns to RM after incidence is solved.

3. Return samples? : In case of incidence is not solved, ask client if sample(s) should be returned. If yes, prepare transportation documents “IMP-811 Sample Return Card” and “IMP-817 Registration of Sample Return”. If not, destroy the samples.

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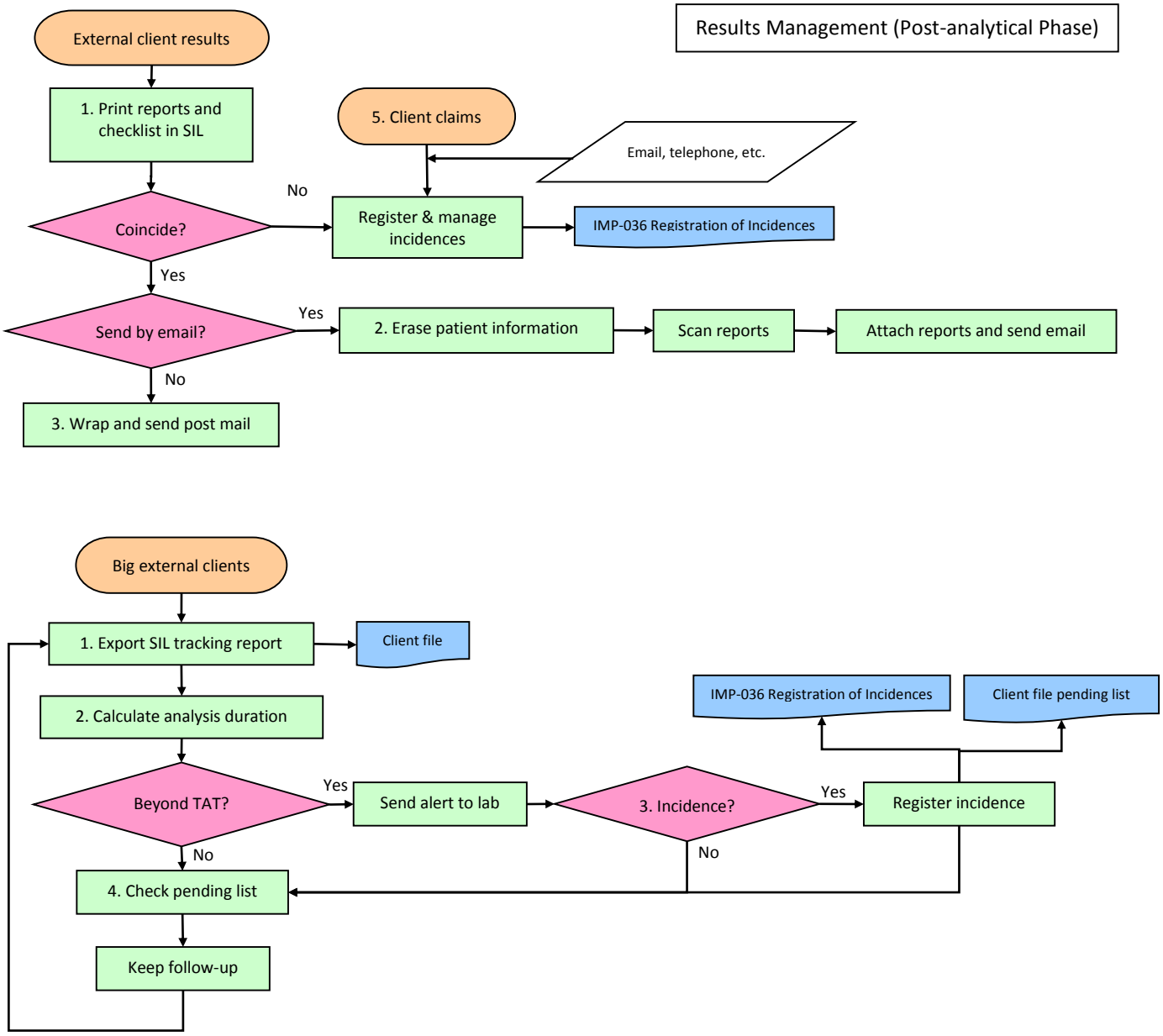

Figure 12. Process Map of Secretary UGC (Post-analytical Phase)

1. Export SIL tracking report: For big clients who have a large amount of requests, export the result tracking report ("Client file") for each of them every day.

2. Calculate analysis duration: In each "client file", calculate the duration of each ongoing test (how many days have passed since sample reception?), and compare with TAT of the test.

3. Incidence? : Get the feedback from corresponding lab, if the delay is caused by any incidence? If yes, record the cause in both "IMP-036 Registration of Incidences" and "Client file pending list".

4. Check pending list: After calculating the duration against TAT, always check the pending list in each client file. Make sure all tests beyond TAT are well traced.

5. Client claims: Receive claims from internal or external clients via email, telephone or other channels, register & manage incidences in “IMP-036 Registration of Incidences” database. Update or close the incidence after a new action is taken for a specific incidence.

4.3.5 Analytical Phase: Extraction Platform

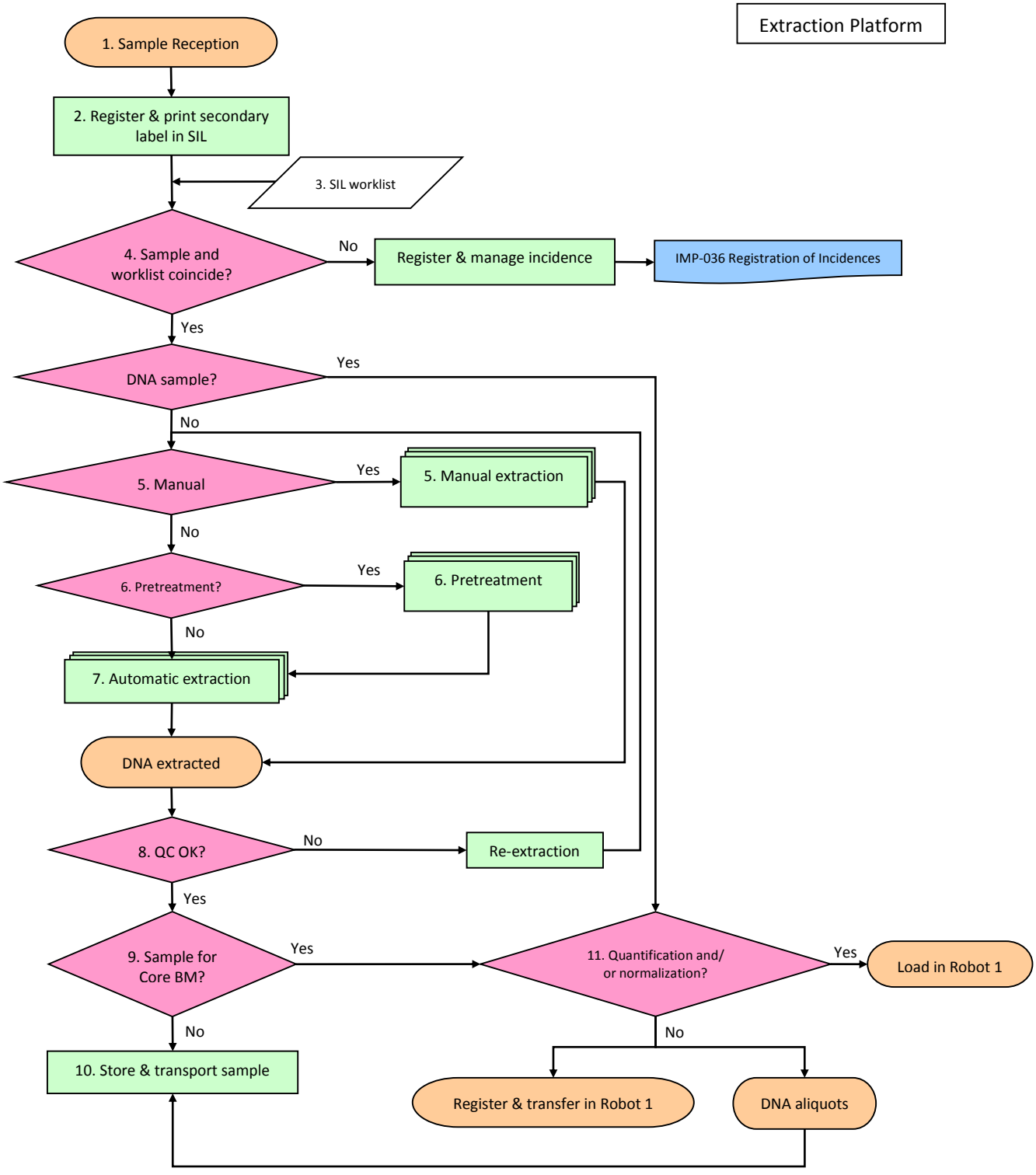

Figure 13. Process Map of Extraction Platform

1. Sample Reception: Usually, samples are transported via pneumatic pipe to Core BM from RM, AP, MIC. The samples are from HCB internal services such as IMM, IBC, etc. or from external labs. Some samples should be transported manually by RM staff due to

special requirements of storage. The sample types include: blood, amniotic fluid, biopsy tissue, dried blood spot, inactivated virus, and DNA or RNA[2] samples.

2. Register & print secondary label in SIL: Technicians scan the primary samples to register sample reception in SIL, in the meantime all the secondary labels (for DNA extracted or necessary aliquots) are automatically printed. Technicians store the samples in the fridge by category depending on sample types or extraction methods. The secondary labels are kept in a particular box until they are pasted in an empty eppendorf which is used for receiving the final product (normally DNA) or prepared aliquots.

3. SIL worklist: Technicians print the worklist from SIL to obtain the list of samples that are planned to be processed.

4. Sample and worklist coincide?: Technicians check the consistency between samples received and worklist. In case of inconsistent sample number or identity, register and manage incidence by contacting different services.

5. Manual extraction?: For the insufficient blood, amniotic fluid, inactivated virus samples, manual extraction will be performed using different protocols.

6. Pretreatment?: For the dried blood spot, biopsy tissue samples, pretreatment is necessary before automatic extraction. E.g. dried blood spot sample needs to be dissolved in liquid for automatic extraction; tissues should be treated with cell lysis reagents in advance.

7. Automatic extraction: In the case of sufficient blood samples or other samples after pretreatment, samples can be loaded to automatic extractors depending on sample type. MagNA Pure 96 (Roche) is for batch DNA extraction of blood samples (Robot 0 is used for sample transfer before and after MagNA Pure 96 processing); MagNA Pure Compact (Roche) is for a small quantity of samples and normally used for dried blood spot and amniotic fluid extraction. For both extractors, it is necessary to load the empty receiving eppendorfs with secondary labels.

8. QC OK?: DNA samples are quantified with spectrophotometer Nanodrop to test concentration and purity; DNA extracted from amniotic fluid should be examined with electrophoresis. The QC results are registered in notebook as well as in PC. In case of QC

[2] In the process map, all RNA samples are omitted due to the little amount of request every year, and all RNA samples are managed manually with special kits

not pass, repeat QC to confirm. If the DNA quality is not good, re-extraction should be performed for the specific sample.

9. Sample for Core BM?: Technicians read destination code in the secondary label to identify the next stop of the extracted DNA – stay in Core BM for sequencing or fragment analysis, or send to services for other tests.

10. Store & transport sample: Technicians pack the samples (sometimes together with QC reports) according to the destinations. Depending on the destinations, technicians send samples via pneumatic pipe or store them in the fridge temporarily, waiting for RM staff manual transportation.

11. Quantification and/ or normalization?: All the DNA samples (including received DNA samples) that stay in Core BM for sequencing or fragment analysis should be quantified and normalized in Robot 1. In case of insufficient DNA (10ul needed for quantification & normalization) or special conditions, DNA samples will be loaded in Robot 1 only for being transferred to 2D tubes, registration or aliquoting.

4.3.6 Analytical Phase: Robot 1 Normalization and Quantification

Robot 1 quantifies and normalizes the extracted DNA in a 2D tube, which goes to Robot 2 for PCR assembly.

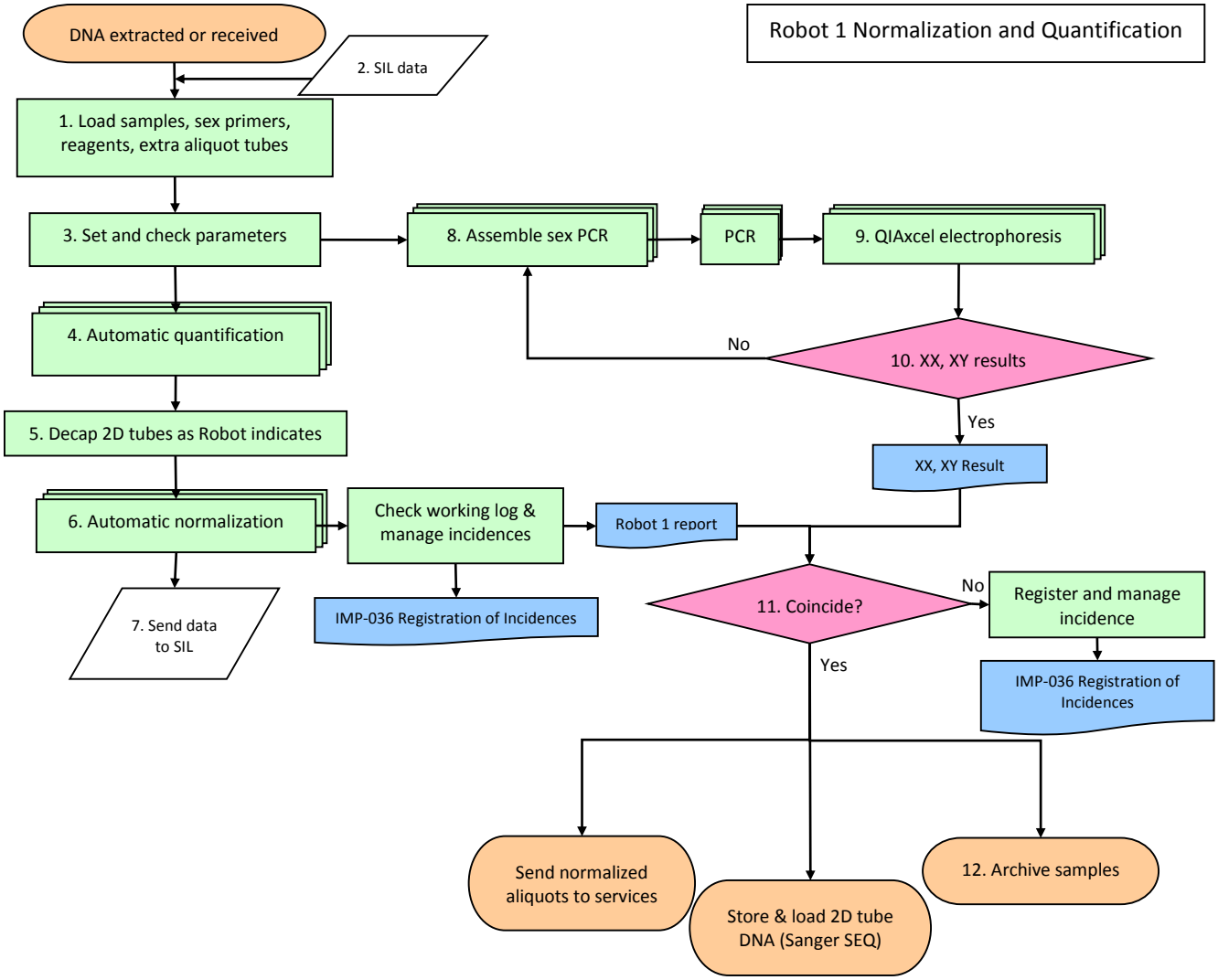

Figure 14. Process Map of Robot 1

1. Load samples, sex primers, reagents, extra aliquot tubes: Load DNA samples with barcoded labels, place in correct positions the 2 prepared primers for sex PCR QC, water and TAQ enzyme. Load PCR plate and empty 2D tubes of Sanger (yellow capped tube with a unique 2D code on the bottom) and NGS (red capped tube with a unique 2D code on the bottom, not applied yet). Load extra tubes with correct labels for aliquoting DNA.

2. SIL data: Robot 1 scans barcode[3] of the DNA samples, and reads from SIL the patient information (sex, Sanger or NGS sequencing).

3. Set and check parameters: Technicians manually select the script to run, either "normalization" or "registration samples only", check or enter the "starting position of dilution plate", "starting position of 2D tubes" (this is automatically set according to the previous run, but should be checked because after a run of "register & transfer", the position is random), "Do sex PCR QC or Not?).

4. Automatic quantification: Robot 1 automatically measures the concentration of each DNA sample.

5. Decap 2D tubes as Robot indicates: Before transferring samples to 2D tubes, Robot 1 asks technicians to manually decap a certain number of 2D tubes. After they are decapped, normalization process can be continued.

6. Automatic normalization: Using the quantification data, Robot 1 automatically calculate and dilute the samples into 50 ng/ul in 100 ul in 2D tubes. Each 2D tube is scanned and linked with a specific SIL barcode, which both identify the unique sample.

7. Send data to SIL: After normalization, Robot 1 sends information to SIL automatically indicating that the normalization is completed "Completed|date|time".

8. Assemble sex PCR: Using 2 primers, Robot 1 automatically assembles PCR reaction for each sample in a PCR 96-well plate.

9. QIAxcel electrophoresis: The sex PCR products are examined in QIAxcel electrophoresis automatically. A blank reference is added automatically.

10. XX, XY results OK? : The electrophoresis result with 1 band indicates the existence of XX chromosomes (female), while with 2 bands indicates XY chromosomes (male). In case of no PCR products are amplified or poorly amplified, repeat the sex PCR.

11. Coincide? : Compare the sex PCR results with the sex report generated from SIL (in Robot 1). If the results do not coincide, find the causes and resolution. This process is only

[3] In Robot 1, barcode of request/ patient is linked with 2D code by Robot 1 programming, and this information is stored in robot DB and is used all through the following processes in Core BM

to avoid large amount of sample contamination or cross-mixing. In case of cross-mixing the samples of the same sex, it cannot be detected.

12. Archive samples: The primary blood samples are archived for 3 months in Core BM. DNA mother samples are kept for 1 week in case repetition is needed, then send to original services. The amniotic fluid, dried blood spot and tissue samples are all consumed during the extraction.

4.3.7 Analytical Phase: Robot 2 PCR Assembly and PCR

Robot 2 assembles PCR of normalized DNA in 96-well plate, which goes to PCR.

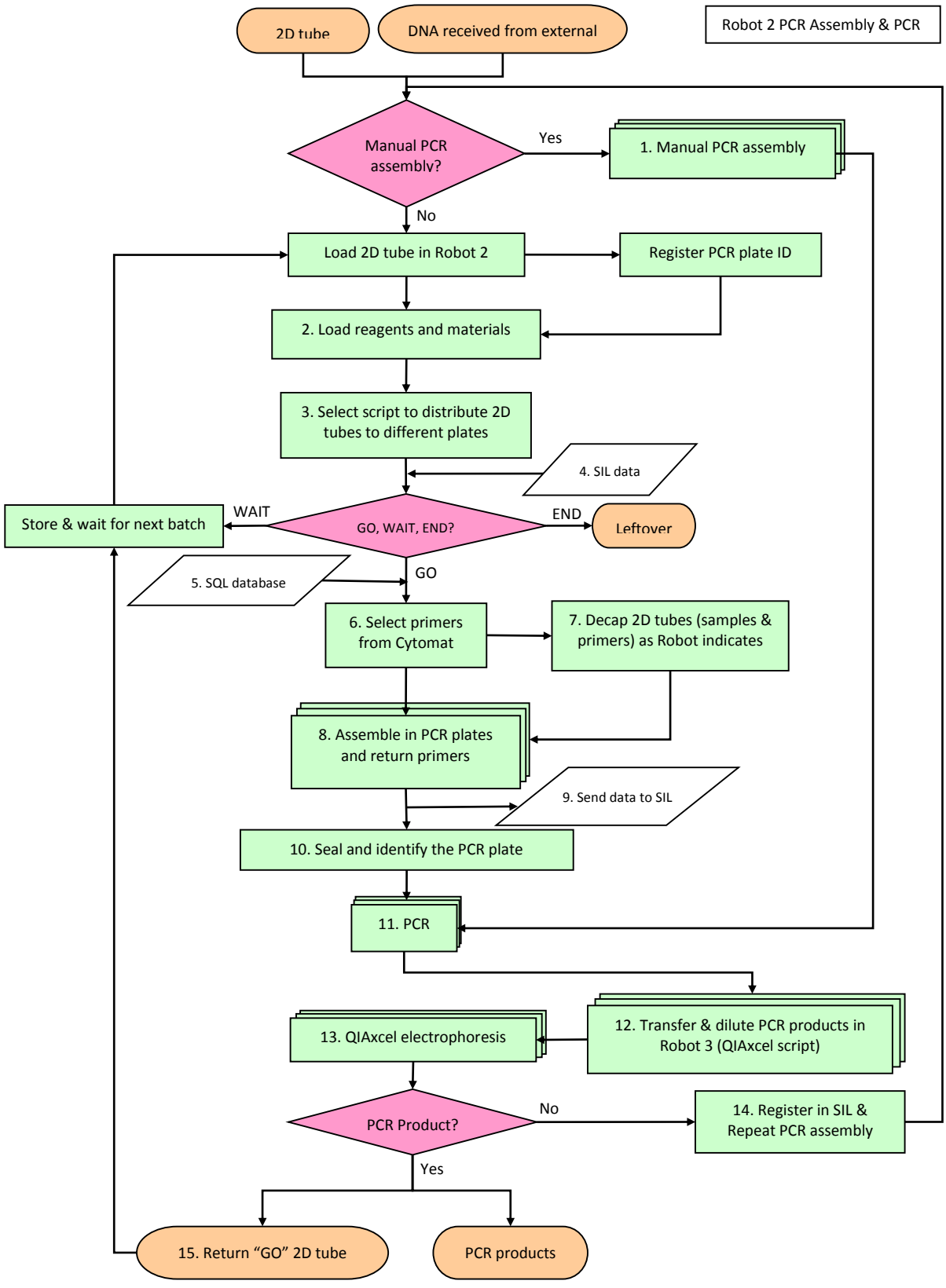

Figure 15. Process Map of Robot 2

1. Manual PCR assembly: This is mainly for MIC virus samples, new primer testing and for PCR repetition, due to the necessity of special protocols, more delicate operations, or small number of samples.

2. Load reagents and materials: The reagents include 4 tubes of water, 4 tubes of AmplitaqGold; the materials include PCR plate, tips, etc. They should be loaded to particular positions in Robot 2.

3. Select script to distribute 2D tubes to different rack: There are 3 racks to receive 2D tubes, “GO”, “WAIT” and “END”.

4. SIL data: Robot 2 asks SIL about the gene(s) to be amplified for each 2D tube according to the DNA sample identity. After samples are registered in SIL, lab physicians check their own worklist and select exons for the requested gene tests. If such exons information exists in SIL, the 2D tube is transferred to “GO” rack to proceed with the PCR assembly; if no information exists in SIL (lab physician has not decided), the 2D tube is transferred to “WAIT” rack and will be loaded again in the next batch; if the test request is closed or canceled by clinical doctors, the 2D tube is transferred to “END” rack and is thrown away after this run.

5. SQL database: For the “GO” samples, Robot 2 asks SQL database what primer(s) will be used for each gene amplification. SQL database corresponds SIL data (request#, gene, exon, cost center) with primer data to match the sample identity with primer position in Cytomat.

6. Select primers from Cytomat: Cytomat outputs selected primers to the primer rack.

7. Decap 2D tubes (samples & primers) as Robot indicates: Before assembling PCR reaction, Robot 2 asks technicians to decap the “GO” samples and selected primers manually.

8. Assemble in PCR plate and return primers: Robot 2 assembles PCR reaction for each exon amplification. Several gene tests can be ordered for one sample (2ul DNA sample is necessary for each amplification). There are 5 wells in the PCR plate that are programmed to be blank control (no sample is transferred to these wells). After assembly completion, primer tubes are scanned and returned to Cytomat.

9. Send data to SIL: After the completion of PCR assembly, Robot 2 sends information to SIL indicating the PCR assembly process is completed “Completed|date|time”.

10. Seal and identify the PCR plate: Seal and mark the PCR plate with the date, sample numbers, plate sequence of the year for easy identification.

11. PCR: Place the PCR plate in thermocyclers, select appropriate programs of PCR.

12. Transfer & dilute PCR products in Robot 3 (QIAxcel script): Load amplified PCR plate in Robot 3, run "QIAxcel" script to transfer a certain volume and dilute the products into a new plate for electrophoresis.

13. QIAxcel electrophoresis: Load the new plate of diluted PCR products in QIAxcel and check if there are amplified products.

14. Register in SIL & Repeat PCR: In case of PCR failure, register in SIL the failure information (i.e. sample ID, which genes are to be repeated), and repeat PCR assembly for that sample, manually or automatically.

15. Return "GO" 2D tube: If the amplification is good, return the "GO" 2D tubes to "WAIT" rack in case of test repetition or other request. The PCR products are loaded in Robot 3 for purification.

4.3.8 Analytical Phase: Robot 3 PCR Purification

Robot 3 purifies the PCR products and prepares for SEQ or AF reactions.

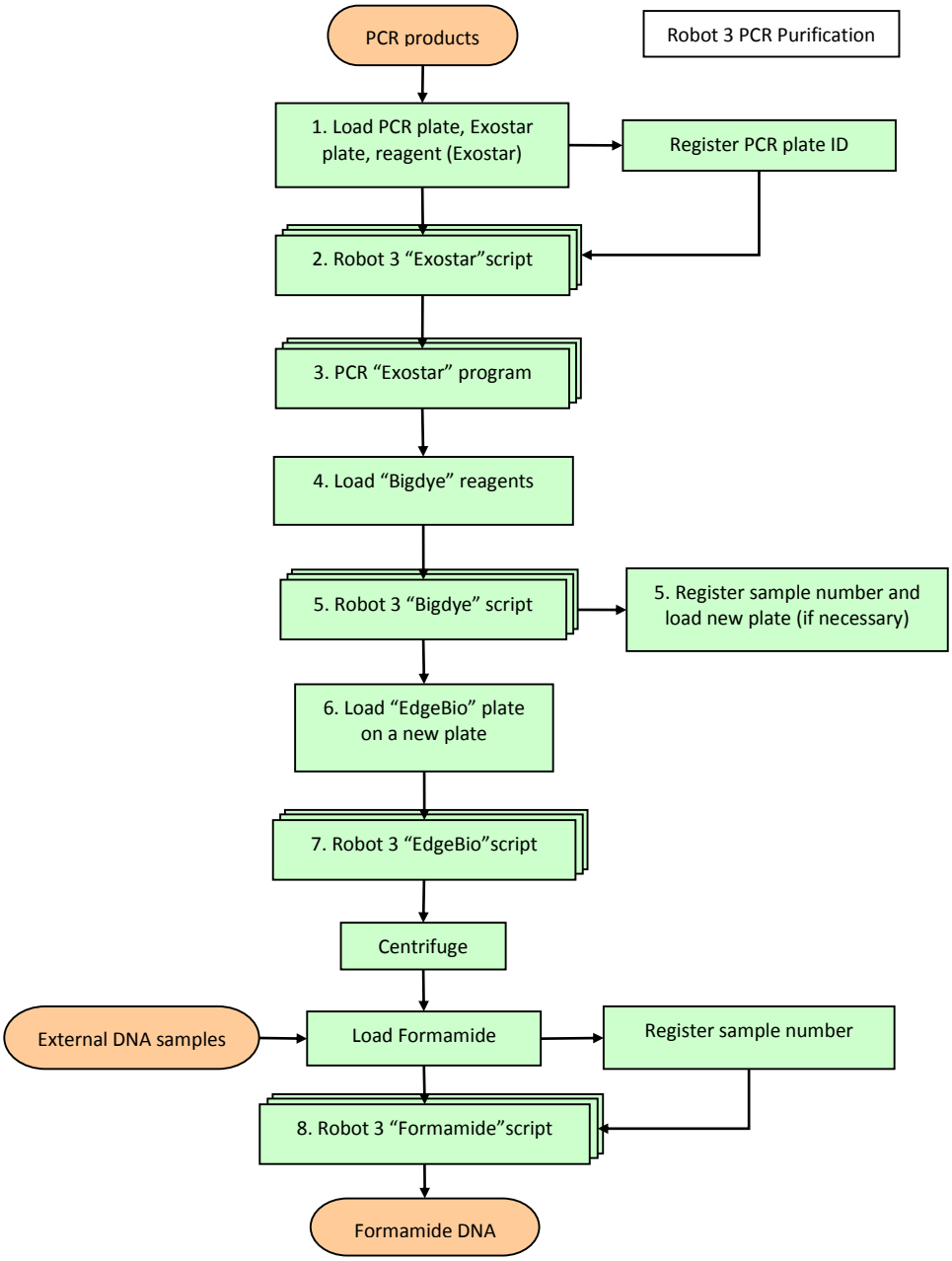

Figure 16. Process Map of Robot 3

1. Load PCR plate, Exostar plate, reagent (Exostar): If the QIAxcel QC result shows good amplification, PCR products can be loaded in Robot 3 for purification. Load a new plate and Exostar reagent to assemble another PCR reaction.

2. Robot 3 "Exostar" script: Run "Exostar" script. Robot 3 transfers 5ul amplified PCR products and prepared "Exostar" 2ul to a new plate "Exostar".

3. PCR “Exostar” program: Seal the Exostar plate and load in thermocycler, run a special PCR program “Exostar” to amplify for 5 min.

4. Load “Bigdye” reagents, new plate (if necessary): Load water, “Bigdye” buffer, “Bigdye”, primer M13 Forward (F) and M13 Reverse (R) in appropriate positions.

5. Robot 3 “Bigdye”script: Run “Bigdye” script. Robot 3 first makes two F and two R Bigdye buffer mixes, and then transfers them into new wells. Robot 3 asks technicians to enter the number of samples. If sample number <=48 (half of the 96-well plate), the “Bigdye” process will transfer half volume of all the Exostar PCR products (3.5ul) to the other empty half of the Exostar plate. If sample number >48, a new plate should be loaded to receive the transferred samples. All the samples are splitted to 2 parts to prepare for the F and R reactions respectively. Robot 3 then mixes F/R Bigdye buffer with samples in each plate. At the end of this process, there are 1 or 2 “Bigdye” plate(s).

6. Load “Edgebio” plate on a new plate: place the “Edgebio” filter gel plate(s) on top of a new plate(s) to receive final samples.

7. Robot 3 “Edgebio” script: Robot 3 transfers all samples in “Bigdye” plate(s) to go through the gel. Technicians collect the final plate(s), cover well and centrifuge.

8. Robot 3 “Formamide” script: Run script “Formamide” to mix with the samples. The samples could be the final samples after centrifuge from Robot 3, or the received DNA samples for Sanger sequencing from external services. The formamide DNAs are ready to be loaded in sequencers.

4.3.9 Analytical Phase: Sanger Sequencing and Fragment Analysis

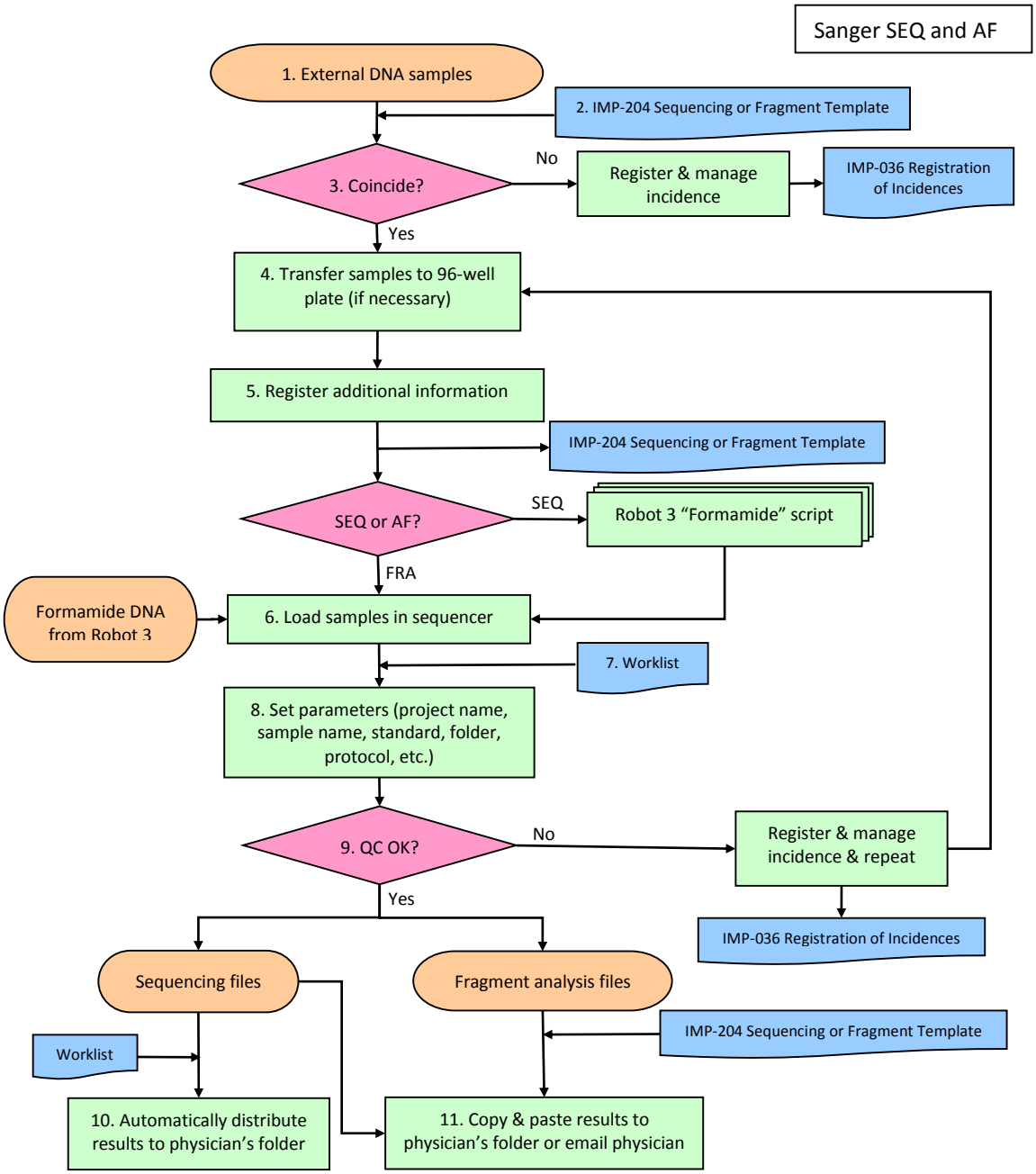

Figure 17. Process Map of Sanger SEQ and AF

1. External DNA samples: Core BM sometimes receives DNA samples that are already well prepared for sequencing or fragment analysis. They are amplified PCR products with buffers added. They can be in individual Eppendorfs or in 96-well plates.

2. IMP-204 Sequencing or Fragment Template: Together with the samples, the test request is sent with the programmed positions of each sample.

3. Coincide? : Technicians check the consistency between the samples received and the request form. This includes the sample number and sample names. Normally sample names are hand-written on each Eppendorfs received, but not on the plate received. On the request form there are always the complete information such as request #, sample number, all the sample names and their programmed positions, requested test, responsible lab physicians, necessary kits and standards (for fragment analysis).

4. Transfer samples to 96-well plate (if necessary): Technicians transfer the samples in Eppendorfs to a plate according to the programmed positions on the request form. Sometimes when combining different requests in one plate to do sequencing in one batch, technicians need to re-program the positions manually. If samples come in plates, there is no need to transfer.

5. Register additional information: Register plate name and other additional information on the request form and mark the plate with plate ID (e.g. F16 means the 16^{th} sequencing plate of the year, F27 means the 27^{th} fragment analysis plate of the year) and date/ time.

6. Load samples in sequencer: Core BM has 2 sequencers for sequencing and 2 for fragment analysis. All of them are with different capacity and can back up for each other.

7. Worklist: There are different ways to obtain the worklist, depending on the previous processing of samples. Robot 3 can automatically output the worklist after processing the purification, which can be modified if other samples are manually added to that plate. Worklist can be copied from SIL electronic request form directly, if a batch of samples is prepared by external services. Also, worklist can be created manually using the particular template for each sequencer.

8. Set parameters: Technicians copy the worklist to the sequencer via a flash disk, enter project name, sample names, select standard, folder, protocol, etc., and run.

9. QC OK?: Technicians check the result quality to make sure the sequencer runs OK, the standards are normal, the blank controls have no DNA sequence, and the result for each gene of each sample is clear and not mixed.

10. Automatically distribute results to physician's folder: Sequencing results for the samples that are registered in Robot database can be automatically distributed to responsible lab physician's online folder according to the naming rule.

11. Copy & paste results to physician's folder or email physician: Other sequencing results should be copied manually to physician's folder or sent by email. All the fragment analysis results must be sent manually by technicians because currently all the fragment analysis is for external DNA samples (not registered in Robot database).

4.4 FMEA Tables

The FMEA study was based on the process maps and detailed steps. The "failure modes" were identified and are listed in FMEA tables (Table 5 to Table 17).

General instruction of FMEA tables:

Step of Process: The steps that bear potential risks. The steps in this column is more general and may include several detailed steps in the process maps in section 0 Process Maps.

Failure Mode: It describes how the failure event could occur within a certain step (risk description).

Immediate Effects: All the possible internal effects that would appear immediately after the failure occurs and before reaching to the patient. These can be the effects on the following processes and/or on the test results. In some cases when the patient is physically involved in the step, the immediate effects can impact patient safety directly.

End Effects: This column only lists the possible effect(s) that could reach to the patient, i.e. the effects on patient safety. The Severity score is evaluated based on the worst effect on patient safety.

Causes: This column lists all possible causes for a certain failure mode. The sources of the causes can vary from the CDB internal departments, the HCB departments or the external clients or organizations. These are the main reference of proposing the actions to treat the risk. The probability is evaluated partially based on the sources of the causes (as well as the available reference data and professional experiences).

Methods of Detection: This column lists the current methods of detecting either the causes (to prevent) or the failure mode (to correct) before the patient safety is affected. The detection can be done either immediately within the current step or in the following steps before the result is delivered to the patient.

Column “S”, “P”, “D”, and “RPN”: See section 3.2 Failure Modes and Effects Analysis (FMEA). The color of RPN score represents the priority of treating the risk.

Action Recommended: These are the proposed actions to treat the risks, i.e. to mitigate the severity, to decrease the probability, and to setup more effective methods and prevent the risk from occurring or reaching to the patient.

4.4.1 Pre-analytical Phase: General

Table 5. FMEA: General

Pre-analytical: General										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
General	Patient accidents (e.g. falling, unconsciousness, etc.) before being extracted	Patient jeopardized	Patient adverse event	Accidents	Undetectable	5	3	5	**75**	First-aid medication in place; First-aid training for all staff especially those in direct contact with patients
General	No electricity	1-All electronic devices stop working 2-All processes delayed	Delayed result	Accident with electricity supply; Hardware error	CDB staff observation	4	1	1	**4**	Prepare back-up plan for electronic processes and maneuver to train staff
General	SIL does not work or works slowly	All CDB sample management processed delayed	Delayed result	Software malfunction	CDB staff observation; Regular maintenance	4	1	1	**4**	IT staff regular check and solve incidences reported (out of SIL working time window)
General	PC does not work	Short delayed processed (back-up PC is used)	No effect	Hardware malfunction	CDB staff observation; Regular maintenance	1	2	1	**2**	No
General	Printer does not work	Short delayed printing (back-up printer is used or wait for recovering)	No effect	Hardware malfunction	CDB staff observation; Regular maintenance	1	2	1	**2**	No

4.4.2 Pre-analytical Phase: Reception of Extraction Center

Table 6. FMEA of Reception CE

Reception CE										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Patient reception	Patient uses other's Health Insurance Card (TSS) as the only identification intentionally	Request activated for another patient	Result assigned to incorrect patient	Patient error	Undetectable	5	1	5	**25**	Use DNI+TSS double check (DNI has photo)
Patient reception	Patient uses other's Health Insurance Card (TSS) as the only identification unintentionally	TSS rejected (other ID documents are used)	No effect	Patient error	Reception staff inspection	1	1	1	**1**	No
Patient reception	The name on request or appointment doesn't match with the present patient	1-Request activated for another patient 2-Request rejected	1-Misleading result 2-No result	HCB administrative staff error (request or appointment distribution error)	Reception staff inspection; Extractor inspection	5	3	1	**15**	Double confirm patient name when distributing request or appointment
Patient reception	The Q-Matic screen or ticket-printer does not function	Short delayed reception	No effect	Hardware malfunction	CDB staff observation	1	2	1	**2**	Prepare back-up plan for queuing process and maneuver to train staff
Patient reception	Patient has conflicting appointment time for blood extraction and doctor consultation	Short delayed reception	Slight patient discomfort	HCB administrative staff error (programming request without checking previous schedule)	Reception staff inspection; Patient complaints	2	2	2	**8**	Program requests and appointments in one system to avoid overlap (or very close) schedule automatically (by system alert)
Patient reception	Patient goes directly to extraction cubicles without activating request	Short delayed request activation	No effect	Patient error; No clear guidance	CDB staff observation; Patient demands	1	3	1	**3**	Give clear instruction on the request; Put clear signs and instructions in reception area

Table 6. FMEA of Reception CE (Continued)

Reception CE										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Patient reception	Patient comes with a closed or already activated request	Request rejected; A new request generated	Slight patient discomfort	Doctor or HCB administrative staff error; Patient error	Reception staff inspection	2	4	1	**8**	Setup alert for doctors when closing the request in SAP and always inform patient of the change. Reception staff always retrieve the activated request from patient
Request order	Test ordered is incorrect for the patient (e.g. a newborn test is ordered for an adult)	Inappropriate test performed	No result (for expected test)	Doctor error (ordering incorrect test)	Extractor inspection	4	3	1	**12**	SAP categorizes test by sample type and sets automatic check to avoid mistake in test selection
Request order	Sample type ordered is impossible to obtain in the extraction center	Test not performed	No result	Doctor error (ordering incorrect type of sample, e.g. body fluids, etc.)	Extractor inspection	4	3	1	**12**	SAP categorizes test by sample type and sets automatic check to avoid mistake in test selection
Request activation	SAP request is not in SIL	Short delayed request activation	No effect	Informatics network malfunction	Reception staff inspection	1	3	1	**3**	No
Request activation	Another inappropriate request is activated (when patient has more than 1 appointed requests in SIL)	Inappropriate test performed	No result (for expected test)	Patient error (patient comes with a request that is programed for a different appointment); Reception staff error	Reception staff inspection	3	2	2	**12**	Display date/time on request for patient and staff to check; Program automatic check of the request date/time
Request activation	Requests are manually merged incorrectly or the merge is incomplete	Test not performed	No result	Reception staff error	Secretary staff review and inspection	4	1	3	**12**	Doctor add tests in existing request if possible to avoid creating a new request; double check after merging
Label management	Not all labels are given to patient	Test not performed	No result	Reception staff error	Coordinator checks report of "Not Received" samples in SIL	4	1	3	**12**	Reception staff check the number of labels after printing
Label management	Another patient's labels are given to a patient	Sample incorrectly identified	Misleading result	Reception staff error	Patient demands; Extractor inspection; Urine Reception staff inspection	5	2	1	**10**	Reception staff double check labels

Table 6. FMEA of Reception CE (Continued)

Reception CE										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Label management	Patient loses the label(s) before extraction	Test not performed	No result	Patient error	Coordinator checks report of "Not Received" samples in SIL	4	3	1	**12**	Program and print sequence number and total number of labels on each label (e.g. 1/3, 2/3, 3/3) for better check
Label management	Material supply of blank labels is used up	Short delayed label printing	No effect	Supplier incident; Reception staff error (miss to order)	Reception staff observation	1	2	1	**2**	No
Extraction priority or category classification	Patient (with a special condition) is assigned an incorrect extraction category ticket (e.g. port-a-cath, urgent)	Short delayed extraction	Slight patient discomfort	Reception staff error (fail to identify the priority, print the ticket by error, deliver the ticket by error); Patient error (not communicates the special needs)	Extractor inspection; Patient demands special extraction	2	4	1	**8**	Information of special patient is highlighted in SIL; always ask patients for prioritized types; not share ticket-printer; differentiate the frequently-pressed button (by color, shape…)
Functional test programming	Incorrect date/ time is registered in the programming excel or in the patient appointment sheet	1-Re-appointment 2-Short delayed extraction	1-Delayed result 2-No effect	Reception staff error	Reception staff inspection	4	2	2	**16**	Develop a printable system to program instead of manual programming in excel
Extraction re-programming	Patient is not informed about a new extraction that has to be performed	Re-extraction not performed	No result	Reception staff error (not proceed with new extraction request)	Undetectable	4	1	5	**20**	Fixed schedule for coordinator (email sender) and reception staff (counter 4) to manage re-extraction request and other special cases; Create an alert function in SIL to remind of pending re-extraction request
Result printing	Result report of another patient is given	Report incorrectly distributed	1-Non-compliance of Personal Data Protection Law (LOPD: Ley Orgánica de Protección de Datos de Carácter Personal) 2-Delayed result obtain	Reception staff error	Patient observation; External doctor inspection	5	1	2	**10**	Staff double-check the identity after printing

4.4.3 Pre-analytical Phase: Extraction Center

Table 7. FMEA of CE

Extraction Center (CE)										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Q-Matic management	Q-Matic does not work	1-No SGC category for patient 2-Short delayed reception and extraction (manual organization of queuing)	Slight patient discomfort	Software malfunction	CDB staff observation	2	2	1	**4**	Prepare back-up plan for queuing process and maneuver to train staff
Q-Matic management	Q-Matic is shut down by mistake during working time	Disorder of reception and extraction	Slight patient discomfort	CDB coordinator error (lack of control)	CDB staff observation	2	1	1	**2**	Software automatically double-confirm, or password control
Q-Matic management	Q-Matic is operated by unauthorized people	Disorder of reception and extraction	Slight patient discomfort	CDB coordinator error (lack of control)	Coordinator observation	2	1	2	**4**	Password control while coordinator leaves
Q-Matic management	Extraction priority is assigned to an inactive cubicle; or different categories with the same priority are assigned to a cubicle	Short delayed extraction	No effect	CDB coordinator error	Coordinator inspection	1	3	1	**3**	Software automatically deactivate the inactive cubicle
Q-Matic management	Extractor leaves the cubicle without closing it off in Q-Matic system	Short delayed extraction	No effect	Extractor error	Coordinator inspection	1	5	1	**5**	Better instruction to extractor
Container identification	Incorrect label (of the same patient) is assigned to a container	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	Extractor error	RM staff inspection; Lab technician inspection	5	2	1	**10**	Training and practicing
Blood extraction	Extractor forgets to use heparin for specific extraction	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	Extractor error	RM staff inspection	5	1	1	**5**	Training and practicing

Table 7. FMEA of CE (Continued)

Extraction Center (CE)										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Blood extraction	Extraction is performed without meeting the requirements of extraction (fasting, medication, diet, time of extraction, etc.)	Test performed with inappropriate sample	Misleading result	Patient error (patient negligence; motivation); Extractor error (not confirm); Instruction not well communicated to patient	Lab physician validation of extreme result; Doctor doubts of result	5	3	4	**60**	Better instruction to patient; extractor double confirms before extraction
Blood extraction	Contaminated materials (e.g. containers contaminated by microorganisms, unexpected substances, etc.) are used in extraction	Test performed with invalid sample	Misleading result	CDB auxiliary staff error (internal quality control of suppliers)	Lab physician validation of result	5	1	3	**15**	No
Blood extraction	Containers used are not in a good condition (broken, opened, not well protected from light, etc.)	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	CDB auxiliary staff error (internal inspection before use)	Extractor inspection; RM staff inspection	5	2	2	**20**	Auxiliary staff checks when re-loading materials for each cubicle; Extractor checks before using
Blood extraction	Insufficient sample is obtained during extraction	Test not performed (new request necessary)	No result	Extractor error; Patient physical condition	Extractor inspection; Lab technician inspection	4	2	1	**8**	Skill and communicational training for extractor
Blood extraction	Patient has adverse event during or after extraction (e.g. allergy, faint, etc.)	1-Patient jeopardized 2-Incomplete extraction	1-Patient adverse event 2-Delayed result	Accident; Patient physical condition; Instruction not well communicated to patient; Extractor error	CDB staff observation	5	1	1	**5**	Skill and communicational training for extractor
Sample storage	Sample is stored in incorrect condition or container (e.g. frozen, 37ºC, 0ºC, light-protected, culture time, etc.)	Test performed with invalid sample	Misleading result	Extractor error; CDB auxiliary staff error; Equipment malfunction	RM auxiliary staff inspection; Lab technician inspection	5	2	2	**20**	Automatic alert for incubators malfunction; staff training (strictly follow the required condition); register start time-end time on tube

Table 8. FMEA of CE (Reception of Urine)

Reception of Urine										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Urine sample collection	Urine sample collection time is incorrect (e.g. "24h" instead of "random")	Test performed with inappropriate sample	Inaccurate result	Patient physical condition; Instruction not well communicated to patient	Urine Reception staff question patient	3	4	3	**36**	Better instruction to patient; staff confirm before reception
Urine sample collection	Insufficient sample of urine is given by the patient	Test not performed	No result	Patient physical condition; Instruction not well communicated to patient	Urine Reception staff inspection; Lab technician inspection	4	2	1	**8**	Better instruction to patient; staff confirm before reception
Urine sample collection	No sample is received from patient (empty containers; patient does not bring 24h urine or leaves without giving sample)	Test not performed	No result	Patient physical condition; Instruction not well communicated to patient	Urine Reception staff inspection; Coordinator checks report of "Not Received" samples in SIL	4	4	1	**16**	Better instruction to patient
Urine sample collection	Container without additives is used to collect "24h urine with additives"	Test performed with inappropriate sample	Misleading result	Patient error; Urine Reception staff error (forgets to add additives) Instruction not well communicated to patient	Lab physician validation of result	5	4	2	**40**	Better instruction to patient; staff confirm before reception
Urine 24h volume calculation	The sum of Urine 24h volume is incorrectly calculated and registered (if >1 bottle)	Incorrect data for calculation of final result	Misleading result (extreme cases)	Urine Reception staff error	Doctor doubts of result	5	1	4	**20**	Staff register immediately after receiving the sample (avoid queuing the samples for later action. It is better to have the patient wait for a while holding their own samples)
Urine 24h volume registration	Urine 24h volume is not registered on diuresis sheets	No data for calculation of final result	Incomplete result	Urine Reception staff error	RM staff inspection; Lab physician validation of result	3	2	1	**6**	Staff register immediately after receiving the sample (without queuing the samples for later action. It is better to have the patient wait for a while holding their own samples)

Table 8. FMEA of CE (Reception of Urine) (Continued)

Reception of Urine										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Urine 24h volume registration	Urine 24h volume is assigned to another patient on diuresis sheets	Incorrect data for calculation of final result	Misleading result (extreme cases)	Urine Reception staff error	Doctor doubts of result	5	1	4	**20**	Staff register immediately after receiving the sample (without queuing the samples for later action. It is better to have the patient wait for a while holding their own samples)
Sample identification	Another patient's label is assigned to the urine sample container	Sample incorrectly identified	Misleading result	Urine Reception staff error	Undetectable	5	1	5	**25**	Training and practicing
Sample aliquoting	Auxiliary staff forgets to aliquot sample from 24h urine	Test not performed	No result	Urine Reception staff error	Coordinator checks report of "Not Received" samples in SIL	4	3	1	**12**	Staff take aliquot immediately after receiving the sample (without queuing the samples for later action. It is better to have the patient wait for a while holding their own samples)
Sample aliquoting	24h urine (if >1 bottle) not mixed before aliquoting	Inaccurate data for calculation of final result	Inaccurate result	Urine Reception staff error	Undetectable	3	2	5	**30**	Staff take aliquot immediately after receiving the sample (without queuing the samples for later action. It is better to have the patient wait for a while holding their own samples)
Urine sample reception	Samples of different patients are cross-contaminated	Test performed with inappropriate sample	Misleading result	Urine Reception staff error	Undetectable	5	1	5	**25**	Staff wear gloves all the time; manage only one sample at a time; keep the working area organized and clean

4.4.4 Pre-analytical Phase: Reception of Samples

Table 9. FMEA of RM

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Sample inspection	Samples for other departments (e.g. AP, MIC Urgent) are accepted by error	1-Request for other departments activated by error 2-Short delayed reception of corresponding departments	No effect	RM reception staff error	RM staff inspection in following processes	1	4	1	**4**	Clear instruction for clients of the exact reception location
Sample inspection	Samples without payment agreement are accepted and sent for test (e.g. samples from unauthorized lab of a client)	Test performed without payment	No result	RM reception staff error	Secretary staff inspection; Finance inspection	4	3	1	**12**	SIL pre-sets accepted clients list
Sample inspection	Insufficient sample is received (container is in good condition)	Test not performed	No result	Human error (extractor error, patient physical condition); Bad communication with patient	Lab technician inspection	4	2	1	**8**	Training for extractor and external clients; Better communication with external clients
Sample inspection	Containers used are not in good condition (broken, opened, not well protected from light, etc.)	Test not performed (sample rejected)	No result	Transportation accident; Container defects	RM staff inspection; Lab technician inspection	4	3	1	**12**	Improve tube protection measures for the frequently broken origins/ clients
Sample inspection	Coagulated sample is received	Test not performed	No result	Extractor error (forgets to add anticoagulants, uses the wrong container, etc.)	RM staff inspection; Lab technician inspection	4	4	2	**32**	Extractor/ clients training (correct tube/ additives)
Sample inspection	Hemolysis sample is received	Test not performed	No result	Storage and transportation condition; Accident; Extractor error (inappropriate extraction)	RM staff inspection; Lab technician inspection	4	4	1	**16**	Extractor/ clients training (correct tube/ additives); strictly follow the storage requirements in all the processing steps

Table 9. FMEA of RM (Continued)

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Sample inspection	Contaminated sample is received (e.g. contaminated by microorganisms, other samples, unexpected substances, etc.)	Test performed with invalid sample	1-Misleading result 2-No result	Storage and transportation condition; Accident; Extractor error (inappropriate extraction)	Lab technician or lab physician validation of result	5	2	3	**30**	Strictly follow the storage requirements in all the processing steps
Sample inspection	Patient name on original sample containers (with original label) does not match the name on the request	1-Test performed with another patient's sample 2-Sample rejected (test not performed)	1-Misleading result 2-No result	Ward nurse or external clients error (mis-place the samples and requests)	RM staff inspection	5	2	2	**20**	Good organization of samples in origins; Clients check before sending; RM staff paste new label without covering the original label so in the following processes staff can double check
Sample inspection	Sample not identified or not identifiable is received	Test not performed (sample rejected)	No result	Ward nurse or external clients error	RM staff inspection; Lab technician double checks in following processes	4	1	1	**4**	Clear instruction for extractors/ clients: how to appropriately label and identify samples, rejecting rule should be respected
Sample inspection	Sample with incomplete information on the label is received (e.g. one patient has multiple samples but without distinguishing the extraction time or order of different sampling)	Test not performed (sample rejected)	No result	External clients error	RM staff inspection	4	2	1	**8**	Clear instruction for clients: how to appropriately label and identify samples, rejecting rule should be respected
Sample inspection	Number of samples received does not match the necessary number on the request	1-Test not performed 2-Delayed sample reception	1-No result 2-No effect	Extractor error; Transportation loss; Label printing error	RM staff inspection	4	2	1	**8**	Reception CE checks label number with request; Design clearer info on request (e.g. total number of tests or tubes); Clients check before sending
Sample inspection	Sample is in incorrect container (i.e. with incorrect additives)	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	Extractor (or other sample collector) error	RM staff inspection	5	4	1	**20**	Training for extractor/ external clients

Table 9. FMEA of RM (Continued)

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Request activation	Request is closed or already activated (from ward or external clients)	Test not performed (sample rejected)	No result	Doctor error; Nurses error	RM staff inspection	4	4	1	**16**	Nurses confirm request is new before taking samples from patient; Pre-set in SIL that closed or activated requests can only be printed with special authorization
Sample identification	Incorrect label (of the same patient) is assigned to a container	1-Test performed with invalid sample 2-Test not performed	1-Misleading result 2-No result	RM reception staff error	RM staff inspection in following processes; Lab technician inspection	5	2	1	**10**	Training
Sample identification	Another patient's label is assigned to the sample	Sample incorrectly identified	Misleading result	RM reception staff error	Lab physician validation of result	5	1	4	**20**	Training
Sample registration in SIL	Sample is not registered in SIL for "Entrada" or "Salida" or is scanned multiple times	Lack of or incorrect traceability in SIL	No effect	RM auxiliary staff error	Undetectable	1	3	5	**15**	No
Sample registration in SIL	Sample label is damaged and/ or unreadable by machine	Sample not automatically registered (manual entry)	No effect	Storage or transportation accident (label is eroded or broken)	RM staff inspection	1	2	1	**2**	Protect the labels with tape when storing in ice water
Request introduction	Incomplete request is received (e.g. patient data incomplete for gene tests; test name not specified; external clients address unclear)	1-Test performed with insufficient information 2-Delayed test 3-No result received	1-Incomplete result 2-Delayed result 3-No result	External clients or HCB doctor error	RM staff inspection; Secretary staff inspection (review process); Lab physician validation of result	4	4	1	**16**	Training for doctor and external clients about completion of request
Request introduction	Requested test does not exist in SIL / catalog	Test not performed (sample rejected)	No result	External clients error; Bad communication with external clients	RM staff inspection	4	3	1	**12**	Unify the catalog for test selectors (in SAP-SIL-Excel library-Clients System) and update regularly; Avoid private communication with external clients
Request introduction	Requested test name does not correspond exactly with that in excel library or HCB catalog webpage	1-Inappropriate test performed 2-Delayed test	1-No result (for expected test) 2-Delayed result	Design of terminology not standardized or consistent	RM staff inspection; Lab physician validation of result	4	3	1	**12**	Unify the catalog for test selectors (in SAP-SIL-Excel library-Clients System) and update regularly; Avoid private communication with external clients

Table 9. FMEA of RM (Continued)

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Request introduction	Request is introduced with some error (patient data, test name, external client data, etc.)	1-Incorrect interpretation 2-Inappropriate test performed 3-No result received	1-Misleading result 2-No result (for expected test) 3-No result report received	RM reception staff error; External client bad hand-writing; Multiple requests on 1 paper	Secretary staff inspection (review process); Lab physician validation of result	5	3	2	**30**	Clients all use SIL interfaces; external request forms are standardized; clear instruction of compulsory information and clear hand-writing; avoid multiple requests on one page
Request introduction	Request is not introduced in SIL	Test not performed	No result	RM reception staff error	RM staff inspection of pending samples; Secretary staff inspection (review process)	4	1	2	**8**	Use one particular desk for big clients with daily multiple requests
Request introduction	Pending samples (including requests) are not managed (e.g. incomplete request pending for secretary communication with client; or multiple >3 request pending for secretary manual introduction)	1-Test not performed 2-Delayed test	1-No result 2-Delayed result	RM reception staff error	RM staff inspection; Secretary staff inspection	4	2	2	**16**	RM first checks the number of samples vs. requests; Specific area identified for pending samples (one request corresponds one bag of samples identified with header label with request number); check and empty the area daily by a responsible person
Sample storage	Sample is stored in incorrect condition (frozen, 37º, 0º, light-protected, culture time, etc.)	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	RM staff error; Storage equipments malfunction	RM staff inspection; Lab technician inspection; Lab physician validation of result	5	2	2	**20**	Automatic alert for incubators malfunction; staff training (strictly follow the required condition); register start time-end time on tube
Processing: Centrifuge	Sample is centrifuged in incorrect condition (e.g. incorrect temperature, duration)	1-Test performed with invalid sample 2-Lab technician centrifuge again	1-Misleading result 2-No effect	RM staff error	Lab technician inspection	5	2	4	**40**	Group the samples in advance according to the centrifuge condition; set a fixed the duration and no need to adjust every time
Processing: Centrifuge	Centrifuge does not work	Short delayed processing	No effect	Hardware malfunction	Lab technician inspection	1	1	1	**1**	Backup plan (centrifuge)

Table 9. FMEA of RM (Continued)

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Processing: Aliquot process	Aliquoting machine does not work (e.g. incorrect setting of the robot "No cap", other incidences e.g. tubes stuck)	1-Short delayed processing 2-Manual aliquot process performed	No effect	Hardware or software malfunction; Aliquoting technician error	Aliquoting technician inspection	1	3	1	**3**	Training for technicians focusing on incidences treatment (to avoid occurrence and shorten resolution time)
Processing: Aliquot process	Aliquoting pipette goes too deep into the primary tube	1-Manual aliquot process performed 2-Inappropriate sample sent to services and lab technician performs aliquoting	No effect	Software design; Aliquoting technician error (not check sample volume before loading samples)	Aliquoting technician inspection; Lab technician inspection	1	3	1	**3**	Set a criteria for samples that can be automatically aliquoted and technician always checks the criteria
Processing: Aliquot process	Sample is cross-contaminated (E.g. a drop of sample falls into another aliquot; not change pipette, etc.)	Test performed with invalid sample	Misleading result	Hardware malfunction	Undetectable	5	1	5	**25**	Aliquoting technician weekly checks the machine working status by close observation
Processing: Manual/ Auto aliquot process	Sample volume is insufficient for aliquoting	Test not performed	No result	Extractor error; Patient physical condition	Aliquoting technician inspection; Lab technician inspection	4	4	1	**16**	A smart system should be developed in SIL to tell: for all the tests of one patient, the minimum volume and number of containers necessary
Processing: Manual aliquot process	Samples of different sampling time points (for the same patient) are mixed by error (for curve test)	Sample inaccurate or cross-mixed	Misleading result	RM aliquoting technician error	Undetectable	5	1	5	**25**	Print on labels a special sign for curve test samples
Processing: Manual aliquot process	Some primary labels cannot generate secondary labels (e.g. prefix 057)	Use primary label instead	No effect	SIL bad mapping	Lab technician inspection	1	3	3	**9**	Fix the programming
Processing: Manual aliquot process	Secondary label of another patient is assigned to an aliquot sample	1-Sample incorrectly identified (same test as expected) 2-Inappropriate test performed (different test from expected)	1-Misleading result 2-No result (for expected patient)	RM aliquoting technician error (during blood or urine aliquoting process)	Undetectable	5	1	5	**25**	Better design in SIL label-printing page (e.g. categorize by sample type: urine or blood, etc.); technician manages one patient sample at a time in a separated rack

Table 9. FMEA of RM (Continued)

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Processing: Manual aliquot process	Secondary label (same patient) of another test/ destination is incorrectly assigned to an aliquot sample	Inappropriate test performed	No result (for expected test)	RM aliquoting technician error (during blood or urine aliquoting process)	Undetectable	4	1	5	**20**	Better design in SIL label-printing page (e.g. categorize by sample type: urine or blood, etc.); technician manages one patient sample at a time in a separated rack
Processing: Manual aliquot process	Sample is cross-contaminated (E.g. Use other patient's sample to make the aliquot sufficient; not change pipette, etc.)	Test performed with invalid sample	Misleading result	RM aliquoting technician error (during blood or urine aliquoting process)	Undetectable	5	1	5	**25**	Double check before using the substitute; Training
Processing: Manual aliquot process	Sample transfer is not performed during manual aliquot process	No aliquot sample	No result	RM aliquoting technician error (during blood or urine aliquoting process)	Coordinator checks report of "Not Received" samples in SIL; Lab technician inspection of worklist	4	2	1	**8**	Clearly label the tube racks during manual aliquoting
Urine 24h volume registration	Incorrect urine 24h volume is registered	Incorrect data for calculation of final result	Misleading result (extreme cases)	RM staff error	Doctor doubts of result	5	2	3	**30**	Double check
Urine 24h volume registration	Urine 24h volume is not register for one patient or urine 24h sheet is lost before registration	No data for calculation of final result	Incomplete result	RM staff error; Transportation loss	Lab physician validation of result	3	2	1	**6**	Double check
Urine 24h volume registration	Registration of urine 24h volume is delayed	Short delayed process	No effect	RM staff error	RM staff inspection	1	3	1	**3**	No
Sample transportation	Pneumatic pipe does not work or work with error	Manual transportation	No effect	Hardware or Software malfunction	CDB staff observation	1	2	1	**2**	Setup pneumatic pipe alert system; Backup plan for human transportation
Sample transportation	Sample is transported under inappropriate condition (internal and external)	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	RM staff error (e.g. some samples cannot be sent by pneumatic pipe; forget to add ice, etc.); Lack of training	RM staff inspection; Lab technician inspection	5	2	2	**20**	Training focusing on frequent occurrence clients

Table 9. FMEA of RM (Continued)

Reception of Samples										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Sample transportation	Sample is lost (during internal processing or transportation from/to other external labs)	No result	No result	RM staff error; Transportation loss	Coordinator checks report of "Not Received" samples in SIL	4	2	1	**8**	Training focusing on frequent occurrence clients
Sample transportation	Sample is distributed to incorrect destination	Short delayed process	No effect	RM staff error (pneumatic pipe code incorrect entry; mis-identify the code, place tubes in incorrect racks, manual transportation by error, etc.)	Lab technician inspection	1	3	1	**3**	No
Sample transportation	Sample is left in incorrect storage equipment in labs (when there is no technician to receive samples)	1-Test performed with invalid sample 2-Test not performed (sample rejected)	1-Misleading result 2-No result	RM staff error	Lab technician inspection	5	2	1	**10**	Better training (which sample requires which condition)
Sample transportation	Sample transportation is delayed	Short delayed process	No effect	RM staff error	RM staff inspection	1	3	1	**3**	Review of collection interval and see if necessary to change; backup staff transports if previous staff not returns on time
Re-extraction request	Email notifying re-extraction is not sent to reception CE (in case of sample invalid or lost)	Test not performed	No result	RM coordinator error	RM coordinator inspection	4	2	4	**32**	Fixed schedule for coordinator (email sender) and reception staff (counter 4) to manage re-extraction request and other special cases; Create an alert function in SIL to remind of pending re-extraction request
Request archiving	Daily requests are archived in incorrect category (e.g. "Derivation"-requests to be sent to external analysis labs; "Incidence"-requests with additional information to be archived for longer time)	Lack of paper traceability (all necessary information is registered electronically in SAP or SIL as backup)	No effect	RM reception staff error	Undetectable	1	2	5	**10**	No

4.4.5 Pre-analytical and Post-analytical Phase: Secretary UGC

Table 10. FMEA of Secretary UGC for Pre-analytical and Post-analytical

Secretary UGC										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Request introduction	Request is introduced with some error (patient data, test name, external client data, etc.)	1-Incorrect interpretation 2-Inappropriate test performed 3-No result received	1-Misleading result 2-No result (for expected test) 3-No result report received	Secretary staff error; External clients bad hand-writing; Multiple requests on 1 paper	Secretary staff inspection (review process)	5	3	2	**30**	External clients all use SIL interfaces; External request forms are standardized; Clear instruction of compulsory information and clear hand-writing; Avoid multiple requests on one page
Request introduction	Request is not introduced in SIL	1-No request in SIL 2-Sample without label 3-Test not performed	No result	Secretary staff error	Secretary staff inspection (review process)	4	1	2	**8**	RM first checks the number of samples vs. Requests; Specific area identified for pending samples (one request corresponds one bag of samples identified with header label with request number); Check and empty the area daily by a responsible person
Request scan	Request is not scanned	Lack of traceability in SIL	No effect	Secretary staff error; Hardware malfunction	Secretary staff inspection (review process)	1	1	2	**2**	No
Request scan	Scanner does not work	Delayed archiving and uploading requests in SIL	No effect	Hardware malfunction	Secretary staff observation	1	1	1	**1**	No
Request inspection	Errors of the manually introduced requests are not identified (patient data, test name, external client data, etc.)	1-Incorrect interpretation 2-Inappropriate test performed 3-No result received	1-Misleading result 2-No result (for expected test) 3-No result report received	Secretary staff error; External clients bad hand-writing	Lab physician validation of result (in case of confusing or incomplete information); Undetectable for other cases	5	2	4	**40**	External clients all use SIL interfaces; External request forms are standardized; Clear instruction of compulsory information and clear hand-writing; Avoid multiple requests on one page
Request inspection	Erroneous modification of request is introduced (patient data, test name, external client data, etc.)	1-Incorrect interpretation 2-Inappropriate test performed 3-No result received	1-Misleading result 2-No result (for expected test) 3-No result report received	Secretary staff error	Lab physician validation of result (in case of confusing or incomplete information); Undetectable (for other cases)	5	1	4	**20**	External clients all use SIL interfaces; External request forms are standardized; Clear instruction of compulsory information and clear hand-writing; Avoid multiple requests on one page

Table 10. FMEA of Secretary UGC for Pre-analytical and Post-analytical (Continued)

Secretary UGC										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Request modification	Incorrect test is added to an activated request (e.g. unexpected test, impossible test, etc.)	Inappropriate test performed	No result (for expected test)	Secretary staff error; Lack of training	Undetectable	4	2	5	**40**	Standardized category or test code to ease communication; Better design of test selection page in SIL; Training
Request modification	A new test which is reasonably added by a doctor is not accepted (when in the lab there is additional sample available for adding such test)	New request needs to be ordered	Delayed result	Secretary staff error; Lack of training	Undetectable	4	1	5	**20**	Program SAP-SIL to automatically search for available samples for the newly requested test
Request modification	Added test is not registered in IMP-815 "Register Modification of Request"	Lack of traceability	No effect	Secretary staff error	Undetectable	1	1	5	**5**	Program SAP-SIL to automatically search for available samples for the newly requested test; doctor can add it directly in SAP
Incidence management	Incidence (internal and external) is neglected (e.g. not managed, not followed-up or not registered or updated in the system)	1-Incidence not treated 2-Incidence pending resolution	1-No result 2-Delayed result	Secretary staff error	External/ internal clients ask for information	4	1	3	**12**	No
Incidence reporting	External/ internal clients are not informed of CDB process changes timely (e.g. certain test cannot be performed for a while)	1-No test performed 2-Delayed test	1-No result 2-Delayed result	Secretary staff error	External/ internal clients ask for result	4	2	2	**16**	Create a client distribution list within each change announcement, instead of separately
Information reporting	Incorrect information is given to the external/ internal clients (e.g. how many/ what type of containers are needed for a test; TAT, etc.)	Incorrect sample management (e.g. invalid sample, insufficient sample, etc.)	1-No result 2-Delayed result	Internal source information error; Communication error; Lack of training	RM staff inspection when receiving samples; External/ internal clients ask for result; Undetectable (for other cases)	4	1	4	**16**	Standardized category or test code; Training to staff and clients about information searching

Table 10. FMEA of Secretary UGC for Pre-analytical and Post-analytical (Continued)

Post-analytical phase: Secretary UGC										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Result management	Result follow-up for external big clients in SIL is not done every day	Delayed tracking	No effect	Secretary staff error	Secretary staff inspection in successive follow-up	1	2	1	**2**	SIL auto report for detecting ALL delayed results
Result management	Alert for the result which is beyond TAT is not sent to services	Not detect incidence timely	Delayed result	Secretary staff error	Secretary staff inspection in successive follow-up	4	2	1	**8**	SIL auto report for detecting ALL delayed results
Result management	Patient private information is not deleted from electronical document	Patient private information received by external organization	Non-compliance of Personal Data Protection Law (LOPD: Ley Orgánica de Protección de Datos de Carácter Personal)	Secretary staff error	Undetectable	5	1	5	**25**	Encrypt all documents to be sent (better automatically)
Result management	Not all results are sent out to external client (by post or email)	No result delivered	1-No result 2-Delayed result	Secretary staff error; Hardware or software malfunction; Transportation lost	Secretary staff inspection (result checklist); External clients ask for result	4	2	1	**8**	Better design of the printing order in SIL (for easy detection and continuation after PC is dead)
Result management	Result is sent to incorrect external client (by post or email)	No result received	1-No result 2-Delayed result	Secretary error; External clients error (incomplete or incorrect information)	External clients ask for result	4	1	3	**12**	Confirm external clients information annually; Compulsory address information on external request form (where to return result/sample)
Request archiving	Request is not archived	Lack of traceability	No effect	Secretary staff error; Hardware malfunction	Secretary staff inspection; External clients ask for result	1	2	3	**6**	No
Sample transportation	Sample is not sent back to external client as required	No sample received by external client to perform test	1-No result 2-Delayed result	Secretary staff error	Secretary staff inspection; External clients ask for samples	4	1	1	**4**	List the external clients that needs sample return; Store the samples in a special place; Check and empty the sample storage place daily by a responsible person

4.4.6 Analytical Phase: Core BM General

Table 11. FMEA of Core BM General

Core BM: General										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
General	No electricity	1-All electronic devices stop working 2-Delayed all processes	Delayed result	Accident with electricity supply; Hardware error	CDB staff observation	4	1	1	**4**	Immediate recovery plan and back-up electricity system
General	Lack of kits, reagents or materials supply	Delayed processes	Delayed result	Technician error (inadequate internal order); Supplier error (incorrect or delayed delivery)	Technician inspection	4	3	1	**12**	Automatic alert in supply registration system, and technician checks regularly
General	Reagents (primers, Amplitaq, Exostar, Bigdye, EdgeBio, formamide, etc.) contaminated by microorganisms, samples, unexpected substances, etc. are used	1-Test performed with invalid sample 2-Reactions failure and immediate repetition	Misleading result	Supplier error (lack of quality control); Technician error (reagents are contaminated during operation)	Technician QC validation	5	1	2	**10**	No
General	Expired reagents are used (primers, Amplitaq, Exostar, Bigdye, EdgeBio, formamide, etc.)	Reactions failure and immediate repetition	No effect	Technician error (lack of inspection)	Technician QC validation; Technician inspection	1	1	2	**2**	Register expiration date directly on reagents on arrival and on aliquots after preparation
General	Auxiliary equipments (centrifuge, incubator, etc.) do not work	Short delayed process and back-up equipments used	No effect	Equipments malfunction; Technician error (lack of maintenance)	Technician observation	1	2	1	**2**	Technician training of immediate recovery; always have back-up equipments
General	QIAxcel, spectrophotometer, electrophoresis equipments do not work	Short delayed process and manual operation	No effect	Equipments malfunction; Technician error (lack of maintenance)	Technician observation	1	2	1	**2**	Technician training of immediate recovery; always have back-up equipments
Network Connection	The connection between SIL and Robot Sample Tracking database is lost	Process interrupted and short delayed process	No effect	Network error	Technician observation	1	2	**1**	**2**	No

Table 11. FMEA of Core BM General (Continued)

Core BM: General										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Sample storage	Sample (blood sample, tissue/biopsy, neonatal blood paper, amniotic fluid, DNA, etc.) storage condition is incorrect	1-Test performed with invalid sample 2-Sample rejected and test not performed	1-Misleading result 2-No result	Storage equipments malfunction; Technician error (storage location; lack of maintenance)	Technician inspection; Technician QC validation	5	2	1	**10**	Clear position identification (labels, fixed position) for each category of sample
Sample storage	Sample (primary, intermediate or final DNA sample) is lost	Test not performed	No result	Technician error (bad labelling); Transportation accident	Technician or lab physician inspection of worklist	4	1	1	**4**	Clear position identification (labels, fixed position) for each category of sample
Sample transportation	Extracted DNA or aliquot primary samples are distributed to incorrect destinations	1-Delayed test 2-Short delayed process and re-distribute	Delayed result	Technician error; Design of secondary label (it needs experience to judge the destination)	Core BM clients inspection	4	2	1	**8**	Design more reader-friendly secondary label (e.g. use "MIC" instead of "017")
Sample transportation	DNA quantification report is not sent back to client as requested (together with the amniotic fluid DNA sample)	Short delayed process and report re-sent	No effect	Technician error	Core BM clients ask for report	1	1	1	**1**	Upload report to shared drive and for client checking
Test repetition	Another patient's sample is selected for repetition	Test performed with other patient's sample	Misleading result	Technician error	Lab physician validation of sequencing result	5	1	4	**20**	For Robot searching: look up in the database manually (which position in which plate is the selected sample), then check if the Robot picks the correct 2D tube
Test repetition	Manual repetition (extraction, PCR, etc.) is not registered in SIL	Lack of traceability in SIL	No effect	Technician error	Undetectable	1	1	5	**5**	No
Archiving	Worklists, quantification results, electrophoresis photos, sex PCR QC results (all intermediate results) are not archived in shared drive or notebooks	Lack of information and traceability	No effect	Technician error	Undetectable	1	1	5	**5**	No

4.4.7 Analytical Phase: Extraction Platform

Table 12. FMEA of Extraction Platform

Extraction Platform: Sample Reception										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Sample inspection	Sample (sample ID, number of samples) and worklist do not match (e.g. IBC neonatal blood sample is not programmed in worklist)	1-Test not performed 2-Delayed test 3-Short delayed process	1-No result 2-Delayed result	SIL worklist bad mapping (incorrect or incomplete); Transportation error or delay; Core BM clients error	Technician inspection	4	3	1	**12**	List clear information in worklist for comparison; check non-receiving samples in worklist and follow-up
Sample inspection	Coagulated blood sample is received	Manual extraction performed	No effect	Extractor error	Technician inspection	1	2	1	**2**	No
Sample inspection	Hemolysis blood sample is received	No effect	No effect	Extractor error; Transportation accident	Technician inspection	1	2	1	**2**	No
Sample inspection	Contaminated sample is received (e.g. contaminated by microorganisms, samples, unexpected substances, etc.)	1-Test performed with invalid sample 2-Reactions failure and immediate repetition	Misleading result	Extractor error; RM staff or client processing error	Lab physician validation of sequencing result	5	1	4	**20**	Remind to the clients about the pre-analytical requirements
Sample inspection	Insufficient primary sample is received	1-Test not performed 2-Manual extraction	No result	Sample obtaining difficulty (patient physical condition; extractor error, etc.)	Technician inspection	4	2	1	**8**	No
Sample inspection	Insufficient DNA sample is received	1-Test not performed 2-Short delayed process	No result	Core BM clients extraction error	Technician quantification check	4	1	1	**4**	Training to the clients; Ask for quantity and concentration information on the request
Label management	Secondary label for DNA (including extra aliquot DNA) is lost	1-Test not performed (no aliquot sent to clients) 2-Short delayed process	1-No result 2-Delayed result	Technician error	Technician inspection; Core BM clients ask for sample	4	2	1	**8**	Always put labels-primary tubes-2ml DNA empty tubes together in 1 bag, if not immediately treated

Table 12. FMEA of Extraction Platform (Continued)

Extraction Platform: Pre-treatment/ Extraction (Automatic and manual)										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
General extraction	DNA extracted manually is insufficient (e.g. amniotic fluid sample)	No more sample available for re-extraction	1-No result 2-Inaccurate result	Primary sample quantity; Extraction accident; Technician error	Technician quantification check	4	3	1	**12**	Training to the clients; Ask for quantity and concentration information on the request
General extraction	DNA extracted automatically is insufficient	1-Extraction repetition 2-Manual extraction	No effect	Sample quantity; Extraction accident	Technician quantification check	1	3	1	**3**	No
General extraction	Requested extraction or re-extraction is not done	Test not performed	No result	Technician error	Technician inspection; Core BM clients ask for result	4	1	2	**8**	Fixed schedule to manage re-extraction request; Create an alert function in SIL to remind of pending request
Manual Extraction/ Pre-treatment	Incorrect kit or reagent is used	1-No more sample available for re-extraction 2-Process failure (immediate repetition)	No result	Technician error	Technician quantification check	4	1	1	**4**	Fixed area and grouped reagents for each operation; Clearly labelling of position of reagents
Manual Extraction/ Pre-treatment	Incorrect volume of reagent is used; incorrect operation of auxiliary equipments (time, rpm, temperature, etc.)	1-No more sample available for re-extraction 2-Process failure (immediate repetition) 3-No effect	No result	Technician error	Technician quantification check	4	1	1	**4**	No
Manual Extraction/ Pre-treatment	Sample and intermediate labels (last 5 numbers hand-written) do not correspond to the same patient	Sample incorrectly identified	Misleading result	Technician error (transfer error; bad labelling)	Technician inspection by chance; Lab physician validation of sequencing result	5	3	4	**60**	Organize samples in short groups during operation; Avoid as much as possible the manual extraction
Manual Extraction/ Pre-treatment	Primary sample (insufficient blood sample, tissue/biopsy, amniotic fluid, etc.) that must be extracted manually is treated automatically	1-No DNA extracted (no more primary sample available for re-extraction) 2-Process failure and immediate repetition	No result	Technician error	Technician observation	4	1	1	**4**	Clear position and organization of samples
Automatic Extraction	Extractors do not work	Delayed test	Delayed result	Hardware malfunction	Technician observation	4	2	1	**8**	No
Sample transfer (Robot 0)	Robot 0 does not work	Manual sample transfer performed	No effect	Hardware malfunction	Technician observation	1	3	1	**3**	No

Table 12. FMEA of Extraction Platform (Continued)

Extraction Platform: Pre-treatment/ Extraction (Automatic and manual)										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Sample transfer (Robot 0)	Necessary secondary tubes are not loaded to receive aliquot of blood samples or DNA samples	No aliquots obtained and test not performed	No result	Technician error	Technician inspection of additional labels; Core BM clients ask for sample	4	3	1	**12**	Always put labels-primary tubes-2ml DNA empty tubes together in 1 bag, if not immediately treated
Automatic Extraction	Accidents occur during automatic extraction (e.g. arm crashing, pipetting problems, etc.)	1-Sample invalid 2-Process failure and immediate repetition	1-No result 2-Delayed result	Hardware malfunction	Technician observation	4	2	1	**8**	Aliquoting technician weekly checks the machine working status by close observation

Extraction Platform: Quantification & Electrophoresis										
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RPN**	**Action Recommended**
Quantification	Quantification spectrophotometer does not work	Short delayed QC process	No effect	Hardware malfunction	Technician inspection	1	1	1	**1**	No
Quantification	Deviation operation of spectrophotometer, e.g. not cleaning, no or incorrect blank measurement, sample with bubble, etc.	1-Test performed with poor quality DNA 2-Incorrect quantification and immediate repetition	No result	Technician error	Technician validation of quantification result; PCR QC; Core BM clients complaint	4	1	1	**4**	Training
Quantification	Another patient's sample is taken to be quantified for QC	Good quantification result assigned to poor quality DNA	No result	Technician error	Core BM clients complaint before TAT; PCR QC	4	1	1	**4**	No
Quantification	Poor quantification result is accepted during technician validation	Test performed with poor quality DNA sample	No result	Technician error	Core BM clients complaint before TAT; PCR QC	4	1	1	**4**	Training
Electrophoresis	Electrophoresis does not work	Short delayed process and back-up equipments used	No effect	Hardware malfunction	Technician observation	1	1	1	**1**	No
Electrophoresis	Deviation operation, e.g. sample not dyed, not adding reference DNA, running overtime, etc.	Incorrect electrophoresis and immediate repetition	No effect	Technician error	Technician validation of electrophoresis result	1	2	1	**2**	Training
Electrophoresis	Sample identity and electrophoresis gel photo do not correspond to each other	Lack of traceability of QC result	No effect	Technician error (manual tracking in excel)	Technician inspection	1	2	4	**8**	Register electrophoresis the sample identity and position in notebook or excel

4.4.8 Analytical Phase: Robot 1 Normalization and Quantification

Table 13. FMEA of Robot 1

Robot 1 Normalization and Quantification											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Automatic normalization	Robot 1 does not work	Normalization not performed (manual normalization)	Delayed result	Hardware malfunction	Technician observation	4	3	1	12	**12**	Technician training of immediate recovery
Automatic normalization	Accident occurs during Robot 1 processing (e.g. arm crashing, pipetting problems, quantification error, etc.)	Incorrect normalization	No result	Hardware malfunction	Technician observation; Robot 1 alert and technician inspection of error log; PCR QC	4	2	1	8	**8**	Technician watches Robot operation; check error log always
Normalization programming	Incorrect processing protocol (script) is selected	Normalization failure (immediate repetition)	No effect	Technician error	Technician observation (Robot 1 alert and cannot proceed)	1	1	1	1	**1**	Set internal logic sequence of the scripts: alert when skip previous steps
Normalization programming	Incorrect parameters are inputted in Robot 1 (e.g. position of starting 2D tubes, position of starting dilution plate, sex PCR Y/N)	Sample wasted (re-extraction if primary sample is left)	No result	Technician error	Technician observation (Robot works with warning or cannot proceed)	4	3	2	12	**24**	Reset "position of 2D tube" as 0 (to clean used 2D tubes and reorganize from 0)
Reagent loading	Incorrect reagents, primers are loaded, or placed in incorrect positions	No amplified products of sex PCR QC (immediate repetition)	No effect	Technician error	QIAxcel QC	1	2	1	2	**2**	Clearly labelling of position and corresponding reagents
Aliquot loading	Necessary secondary tubes are not loaded to receive aliquot DNA sample	Test not performed (no aliquots)	No result	Technician error	Technician inspection of additional secondary labels; Core BM clients ask for sample	4	3	1	12	**12**	Robot 1 checks with SIL the number of extra aliquots and alert
Sample registration	Incorrect barcode number of sample is entered manually (request#) and is linked to a 2D tube	Sample incorrectly identified	Misleading result	Technician error	Undetectable	5	2	5	10	**50**	Technician double check after scanning or manual introduction
Manual decapping	Less 2D tubes are decapped than needed	Sample wasted (re-extraction if primary sample is left)	No result	SIL bad mapping; Network error; Technician error	Technician observation (Robot works with warning or cannot proceed)	4	2	1	8	**8**	No
Robot data output	No data is transferred to SIL after normalization completed	No traceability in SIL	No effect	Network error	Technician inspection when necessary	1	1	1	1	**1**	No

4.4.9 Analytical Phase: Robot 2 PCR Assembly and PCR

Table 14. FMEA of Robot 2

Robot 2 PCR Assembly & PCR											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Automatic assembly	Robot 2 does not work	PCR reaction cannot be assembled automatically (manual assembly)	Delayed result	Hardware malfunction	Technician observation	4	2	1	8	**8**	Technician training of immediate recovery
Automatic assembly	Accident occurs during Robot 2 processing (e.g. arm crashing, pipetting problems, etc.)	Incorrect PCR assembly	No result	Hardware malfunction	Technician observation; Robot 2 alert and technician inspection of error log; Technician validation of sequencing quality	4	2	1	8	**8**	Technician watches Robot operation; check error log always
Reagent loading	Incorrect or inappropriate concentration of reagents is loaded (Amplitaq, water), or place reagents in incorrect positions	Incorrect PCR assembly and always sufficient DNA sample for immediate repetition	No effect	Technician error	QIAxcel QC	1	2	1	2	**2**	Clearly labelling of position and corresponding reagents
Sample registration	Not all 2D tubes in one plate are scanned and read into sample tracking database	Sample left in "WAIT" rack and no PCR assembly performed	Delayed result	Hardware malfunction	Technician inspection of SIL worklist	4	2	3	8	**24**	Robot tells the number of 2D tubes after reading and technician checks
SIL data input	Input information from SIL (e.g. exons) is delayed	Delayed PCR	Delayed result	Physician entry delayed; Network error	Technician inspection of sample list in database	4	3	1	12	**12**	Original request contains all information necessary (test, gene, exon…)
SIL data input	Information from SIL (e.g. exons) is incorrect	1-Inappropriate exon amplified 2-No primer is found	No result	Physician entry error	Robot 2 alert; Physician validation of sequencing result	4	3	1	12	**12**	Doctor training of ordering tests
Primer selection	Primer selected (from Cytomat) for exon amplification is incorrect	Inappropriate exon amplified	No result	Technician error (transfer error when diluting primer into 2D tubes; primer database registration error/ not updated timely/ changed by error, etc.)	Physician validation of sequencing result	4	2	1	8	**8**	Scan and check again before return to Cytomat; Technician check primer list regularly

Table 14. FMEA of Robot 2 (Continued)

Robot 2 PCR Assembly & PCR											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Primer selection	Primer is not found in Cytomat or primer is insufficient	Short delayed process	No effect	Technician error (old primer insufficient or changed; new primer not prepared); Primer database error	Robot 2 alert and technician inspection of error log	1	2	1	2	**2**	Cytomat checks in advance according to SIL request
2D tube distribution	2D tube is assigned to "END" incorrectly (according to SIL)	1-Test not performed (request closed or canceled) 2-2D tube DNA aliquot discarded	No result	Network error; Request is closed by physician incorrectly	Undetectable	4	2	5	8	**40**	No
Automatic assembly	One DNA sample is insufficient for all multiple amplifications requested (100ul DNA in one 2D tube is sufficient for 50 amplifications)	No more DNA sample for repetition PCR assembly	No result	Insufficient sample received; DNA Extraction error	PCR QC	4	2	1	8	**8**	No
Robot data output	No data is transferred to SIL after assembly completed	No traceability in SIL	No effect	Network error	Technician inspection when necessary	1	1	1	1	**1**	No
Manual PCR assembly	Incorrect protocol or inappropriate volume or concentration of kit/ reagent/ primer is used	1-Inappropriate exon amplified 2-PCR assembly failure and not always sufficient DNA for repetition 3-Short delayed PCR and immediate repetition	No result	Technician error	QIAxcel QC; Physician validation of sequencing	4	2	1	8	**8**	No
Manual PCR assembly	Sample is transferred to incorrect position in the PCR plate (when there are multiple samples in a batch)	Sample incorrectly identified	Misleading result	Technician error (sample transfer; bad labelling)	Undetectable	5	2	5	10	**50**	Use a notebook (not excel) to register the position of samples, always check the notebook during the manual assembly. Mark the rack or plate with a starting position

Table 14. FMEA of Robot 2 (Continued)

PCR											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
PCR	Incorrect processing program is selected	PCR failure and immediate repetition	No effect	Technician error	QIAxcel QC	1	2	1	2	**2**	No
PCR	PCR works with error	PCR failure and immediate repetition	No effect	Hardware malfunction	QIAxcel QC	1	1	1	1	**1**	Regular calibration and maintenance
PCR	Manually prepared plate or samples are not identifiable	PCR result not identifiable and immediate repetition	No effect	Technician error	Technician inspection	1	2	1	2	**2**	Put a notebook beside and register each plate and start time
PCR	Plate is not sealed	PCR failure and immediate repetition	No effect	Technician error	Technician inspection; QIAxcel QC	1	1	1	1	**1**	No
PCR	PCR is not done	Delayed test	Delayed result	Technician error	Technician inspection; Core BM clients ask for result	4	1	2	4	**8**	Require traceability for each step
QIAxcel QC	QC result is mis-matched with another sample	Inappropriate sample is proceeded when no amplified product and repetition after sequencing result obtained (if sample sufficient)	1-No result 2-Delayed result	Technician error (sample transfer)	Technician validation of sequencing quality	4	1	1	4	**4**	No
QIAxcel QC	Negative control is contaminated (e.g. by microorganisms, samples, unexpected substances, etc.)	1-Contaminated sample is proceeded 2-Inappropriate sample is proceeded and repetition after sequencing result obtained (if sample sufficient)	1-No result 2-Delayed result	Technician error	Technician validation of sequencing quality	4	2	2	8	**16**	No
QIAxcel QC	QIAxel does not work	Manual electrophoresis QC performed	No effect	Hardware malfunction	Technician observation	1	2	1	2	**2**	No

4.4.10 Analytical Phase: Robot 3 PCR Purification

Table 15. FMEA of Robot 3

Robot 3 PCR Purification											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Automatic Purification	Robot 3 does not work	Manual purification performed	No effect	Hardware malfunction	Technician inspection	1	2	1	2	**2**	Technician training of immediate recovery
Automatic Purification	Accident occurs during Robot 3 processing (e.g. arm crashing, pipetting problems, etc.)	Incorrect purification	No result	Hardware malfunction	Technician observation; Robot 3 alert and technician inspection of error log; Technician validation of sequencing quality; Physician validation of sequencing result	4	2	1	8	**8**	Technician watches Robot operation; check error log always
Sample registration	PCR plate loaded for purification does not correspond to the plate ID introduced (manually entered or scanned) in Robot 3	Sequencing report incorrectly assigned to the samples in another plate (sequencing result is correct)	No effect	Technician error; Network error; scanner error	Technician validation of sequencing report	1	1	1	1	**1**	Double check
Reagent loading	Incorrect purification reagents (Exostar, Bigdye, M13, Formamide, etc.) is loaded, or placed in incorrect positions	1-Sequencing failure and immediate repetition from PCR amplified products (always sufficient sample) 2-Poor sequencing quality	No effect	Technician error	Technician validation of sequencing quality; Physician validation of sequencing result	1	2	1	2	**2**	Clearly labelling of position and corresponding reagents
Purification programming	Incorrect processing protocol (script of Exostar, Bigdye, Formamide) is selected	Robot cannot work	No effect	Technician error	Technician observation; Robot alert and technician inspection of error log	1	2	1	2	**2**	Set internal logic sequence of the scripts: alert when skip previous steps; traceability of PCR plate in Robot database
Purification programming	Not all steps of purification is completed (skip 1 or 2 steps, e.g. not add formamide), or the script sequence is incorrect	1-Sequencing failure and immediate repetition from PCR amplified products (always sufficient sample) 2-Poor sequencing quality	Acceptable result with minor defect	Technician error	Technician validation of sequencing quality; Physician validation of sequencing result	2	2	1	4	**4**	Set internal logic sequence of the scripts: alert when skip previous steps; traceability of PCR plate in Robot database

Table 15. FMEA of Robot 3 (Continued)

Robot 3 PCR Purification											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Purification programming	Number of samples entered is more than actual number (>48 use 2 plates to assemble sequencing reaction; <48 use 1 plate is enough)	No effect	No effect	Technician error	Technician observation	1	1	1	1	**1**	No
Purification programming	Number of samples entered is less than actual number (E.g. enter 48 for 49 samples, Robot uses 1 plate to assemble sequencing reaction, so sample #49 is mixed with sample#1; or formamide is not done for some samples)	1-Sample cross-contaminated 2-Sample assembly not completed	No result	Technician error	Technician validation of sequencing quality; Physician validation of sequencing result	4	2	2	8	**16**	Number of samples can be known from the database of R2 (when PCR plate ID is entered) and compare with manual entry? Modification requires confirmation.
Sample collection	The final sample receiving plate is not placed under EdgeBio to collect the sample	Sample wasted and immediate repetition from PCR amplified products	No effect	Technician error	Technician observation	1	1	1	1	**1**	No
Centrifuge	Final sample receiving plate is not centrifuged	1-Sample wasted and immediate repetition from PCR amplified products 2-No sample in the receiving plate and centrifuge again	No effect	Technician error	Technician observation	1	1	1	1	**1**	No
Robot data output	No data is transferred to SIL after purification completed	Lack of traceability of process	No effect	Network error	Technician inspection when necessary	1	1	1	1	**1**	No

4.4.11 Analytical Phase: Sanger Sequencing and Fragment Analysis

Table 16. FMEA of Sanger SEQ and AF

Sanger Sequencing & Fragment Analysis											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Sequencing & Fragment Analysis	All sequencers do not work	Delayed test	Delayed result	Hardware malfunction	Technician observation	4	1	1	4	**4**	Technician training of immediate recovery
External sample inspection	DNA sample preparation by external clients does not meet the sequencing criteria (e.g. contaminated, low concentration or purity)	Test performed with invalid sample	1-No result 2-Delayed result	Core BM clients preparation error	Technician validation of sequencing quality; Physician validation of sequencing result	4	4	2	16	**32**	No
External sample registration	Sample tube/plate ID or quantity received do not correspond to the request (IMP-204 in SIL)	Delayed test (confirmation or re-extraction is needed)	Delayed result	Core BM clients error (handwritten sample name not identifiable; transportation, request programming error)	Technician inspection	4	2	1	8	**8**	No
External sample registration	Sample tube or plate received is not identified or poorly identified	Delayed test (confirmation or re-extraction is needed)	Delayed result	Core BM clients error (handwritten sample name not identifiable or no label)	Technician inspection	4	2	1	8	**8**	Unify plate ID corresponding to each PCR plate in Robot 2
External sample transfer	More than 1 sample is transferred to the same position in a plate	1-Test performed with invalid sample 2-Repetition after physician validation	1-No result 2-Delayed result	Technician error (overlapped programming, sample transfer)	Technician validation of sequencing quality; Physician validation of sequencing result	4	2	2	8	**16**	No
External sample transfer	No sample is transferred to a programmed position in a plate	1-Test not performed 2-Repetition after physician validation	1-No result 2-Delayed result	Technician error (sample transfer)	Technician validation of sequencing quality	4	2	1	8	**8**	No
External sample transfer	Sample is transferred to erroneous position (not consistent with the programmed position)	Sample incorrectly identified	Misleading result	Technician error (sample transfer)	Undetectable	5	2	5	10	**50**	No
External sample transfer	Insufficient volume is transferred to the sequencing plate	Sequencing failure and immediate repetition from sample transfer (if sample sufficient)	No result	Technician error (sample transfer)	Technician validation of sequencing quality	4	2	1	8	**8**	No

Table 16. FMEA of Sanger SEQ and AF (Continued)

Sanger Sequencing & Fragment Analysis											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Worklist input	Worklist imported to a specific sequencer is not readable	Immediate correction of template or format	No effect	Technician error (inappropriate template is used; incorrect entry or modification); Robot 3 worklist output error	Technician observation	1	1	1	1	**1**	Modification to auto worklist is not recommended. Check sample numbers with worklist
Worklist input	Sequencer proceeds with incorrect worklist (sample ID, position, etc.)	Result incorrectly assigned	Misleading result	Technician error (manual entry or modification error); Robot 3 worklist output error; Core BM clients worklist error	Doctors or Core BM clients doubt of result (e.g. a "recessive autosomal disease" is only possible when phenylketonuria?)	5	2	4	10	**40**	Modification not recommended. Double check
Worklist input	Sequencer proceeds with incomplete worklist	Test not performed for some samples and immediate repetition of sequencing	No effect	Technician error (manual entry or modification error); Robot 3 worklist output error; Client worklist	Technician validation of sequencing report	1	2	1	2	**2**	Modification to auto worklist is not recommended. Check sample numbers with worklist
Sequencing programming	Incorrect sample position is selected to perform sequencing	Sequencing disorder and immediate repetition	No effect	Technician error	Technician validation of sequencing report	1	2	1	2	**2**	No
Sequencing programming	Incorrect assay/ script is selected	1-Sequencing failure and immediate repetition if sample sufficient 2-Poor sequencing quality for physician validation	No result	Technician error	Technician validation of sequencing quality	4	2	1	8	**8**	No
Sequencing & Fragment Analysis	Negative quality control is not done or inappropriately interpreted (e.g. contaminated blank control is not detected)	Poor sequencing quality for physician validation	No result	Technician error; Lack of training	Physician validation of sequencing result	4	1	2	4	**8**	No

Table 16. FMEA of Sanger SEQ and AF (Continued)

Sanger Sequencing & Fragment Analysis											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Sequencing & Fragment Analysis	Accident occurs during sequencing process	1-Sequencing failure and immediate repetition if sample sufficient 2-Poor sequencing quality for physician validation	No result	Hardware error	Technician observation; Technician validation of sequencing quality; Physician validation of sequencing result	4	2	1	8	**8**	No
Sequencing & Fragment Analysis	Sequencing result is sent to incorrect physician	1-Delayed physician validation 2-Short delayed process	Delayed result	Technician error (manually sent; Select incorrect naming rule/ results folder); Sequencer automatic distribution error	Physicians ask for result	4	2	2	8	**16**	No
Sequencing & Fragment Analysis	Result is not sent out	1-Delayed physician validation 2-Short delayed process	Delayed result	Technician error; Sequencer automatic distribution error	Technician inspection of pending report; Physicians ask for result	4	2	2	8	**16**	No
Sequencing & Fragment Analysis Repetition	Sample after addition of formamide for a long time is used for repetition	1-Sequencing failure and immediate repetition if sample sufficient 2-Poor sequencing quality for physician validation	No result	Technician error	Technician validation of sequencing quality	4	2	1	8	**8**	No

4.4.12 Post-analytical Phase: Physician Validation and Sample Archiving

Table 17. FMEA of Physician Validation and Sample Archiving (Post-analytical)

Post-analytical											
Step of Process	**Failure Mode**	**Immediate Effects**	**End effects**	**Causes**	**Methods of Detection**	**S**	**P**	**D**	**RL**	**RPN**	**Action Recommended**
Physician validation	Sequencing result validation is incorrect	Incorrect interpretation	Misleading result	Physician error	Doctors doubt of result	5	1	4	5	**20**	Double check
Physician validation	Validation report is assigned to another patient in SIL	Report incorrectly identified	Misleading result	Physician error	Doctors doubt of result	5	1	4	5	**20**	SIL automatically assign report
Sample archiving	Sample is not archived appropriately (e.g. discarded or stored in incorrect condition, etc.)	1-No sample for repetition 2-Poor quality of sample for repetition	Patient discomfort	Technician error	Undetectable	2	1	5	2	**10**	No

4.5 Results Summary and Discussions

4.5.1 FMEA Results and Discussions

216 Risks were identified for all the phases and departments. Among them 50% were from pre-analytical phase, 47% were from analytical phase (Core BM), and only 7% were from post-analytical phase. Table 18 summarizes the risks distribution across departments.

Table 18. FMEA Summary

	Pre-analytical			Analytical	Post-analytical	
Risk	Reception CE	RM	Secretary	Core BM	Secretary	**Sum**
High	2	0	0	4	0	**6 (3%)**
Medium	3	6	3	3	0	**15 (7%)**
Minor	22	22	5	22	2	**73 (34%)**
Low	22	19	4	72	5	**122 (56%)**
Sum	**49**	**47**	**12**	**101**	**7**	**216**
	108 (50%)			**101 (47%)**	**7 (3%)**	**216 (100%)**

21 risks were ranked as high or medium to be treated with priority, which mainly focused on sample quality and manual procedures. Sample quality is crucial for a good result. To control the necessary storage condition, the correct extraction procedure, timely and secure transportation before or during the analysis are the actions to ensure sample quality. Manual procedures of identifying and labelling patients and samples in both pre-analytical and analytical phases are the weakest links in overall workflow: they bear the catastrophic effects and most of them are undetectable. Especially when processing the samples by batch, the technicians can easily cross the sample identity thus the result would be totally incorrect and misleading. Since the Core BM is equipped with 4 robots handling all the samples and procedures, to avoid as much as possible the manual procedures and to establish a smarter labelling system with clear traceability are the most important actions to be taken.

Actions were proposed to treat as many as possible the identified risks. All the actions regarding the 21 high and medium risks were recommended to the management team for immediate implementation. Considering the cost-effective requirements, there are some common actions for different risks, which will reduce significantly the overall RPN, such as:

1) Program the informatics system in a smarter way to avoid human errors in all the TTP processes:
    a. The labels in SIL and the request forms in SAP can be designed more user-friendly, so that they have all the necessary information. E.g.: to list the total number of labels on each label and to list the total number of sample tubes on the request form will make the laboratory staff to read more easily.
    b. Gradually popularize the use of SIL interface among external clients. This will reduce the probability of managing manual requests of various forms, which bears many high risks.
    c. Improve the robots' capability of information exchange with SIL, so as to avoid manual entry of sample numbers or other information during the automatic processes.
2) Patient and client communication about the sample requirements is the key to ensure sample quality and quantity. To give the patient necessary instructions before taking samples and to inform client of the acceptable sample criteria will largely reduce the probability of receiving insufficient or inadequate samples.
3) Clearly label and group the samples is critical to ensure all the samples are managed in an expected way and not cross-mixed.
4) For all the laboratory technicians, the training of immediate recovery of the equipments or robots they operate is the most effective way to avoid sample waste and delay of result.

4.5.2 Methodology Discussions

This risk assessment study lasted for 6 months and is still ongoing in terms of risk treatment and continuous monitoring. Compared to previous studies, it covered full TTP scope and thus seemed time-consuming. 2 months were spent in observing the laboratory processes. In risk management, it is an issue that the task performer is not familiar with the processes. To study them is time-consuming and heavy work which however is the premise of better assessment and management. Sometimes the study cannot be comprehensive due to time limitation, which could impact the quality of the risk assessment. More efficiently and effectively, the risk identification part can be performed by an expert who already possesses the knowledge of a certain process. So it is a good approach to train the experts to have a basic risk-based mindset to contribute in risk management and quality management. In such

context, the quality manager should only be a facilitator of the team and provide expertise in methodologies. In a larger scope, everyone who works in a clinical laboratory should bear the quality and risk management in mind, so as to contribute in their daily work.

Risk assessment is subjective and may vary if performed by different teams [43]. The scoring criteria, the RPN matrix, the definition of each terminology, etc. none of them has an existing standard or reference. To be practical and meet the needs of the organization is the only and ultimate principle. In order to achieve the effective goal, an experienced and cross-functional team is the key of success. In this study, the most challenging part was to define and apply the criteria of S, P and D. In multiple rounds of reviews, the criteria were modified several times and finally the team reached to an agreement.

Previous studies applied FMEA to simple processes and the criteria of S, P and D are simple. While performing a large scope risk assessment such as TTP scope, another approach could be suggested: to define customized criteria for different processes. E.g. in this study, for pre-analytical area, P was defined as the occurrence per patient, while for analytical phase, it was defined per sample. Similarly, it would also be possible to define different criteria S based on the outcome of each general process. This may result in more work but the assessment will be more precise and effective.

5 CONCLUSIONS

From the risk assessment study we have performed for the clinical laboratory in a TTP scope, we conclude that:

1) It is clear that the laboratory errors and delays can potentially have huge impact on patient safety by means of delivering laboratory results as diagnostic references. Among the 21 prioritized risks, 19 bear the severity score 4 or 5. Which means these risks of higher probability and lower detectability can result in critical or catastrophic effects on patient safety. The most critical and weakest link in TTP is the manual sample identification procedures, in which samples are labeled or identified manually. It is necessary to avoid as much as possible the manual processes and to create a smarter sample labelling system.
2) Risk assessment is a powerful tool to avoid or mitigate the errors and delays in a clinical laboratory. It is an important tool in the laboratory quality management system that ensures the reliability of test results and contributes to assure patient safety. It is the foundamental step of the dynamic risk management system. The improvement is expected after the implementation of the proposed actions, and the risks may vary during continuous improvement, which should be monitored and reviewed regularly.
3) FMEA is successfully applied to perform a risk assessment for the clinical laboratory TTP processes. It enables to identify potential process failures before they occur and helps to prioritize risks in the weakest links, where improvement actions are needed. The methodology can be customized according to different context to meet different needs.
4) To our knowledge, this is the first study in Europe that applied FMEA in a hospital clinical laboratory in the TTP scope, i.e. pre-analytical, analytical and post-analytical phases of Core BM. It has laid the foundation of the risk management system in the laboratory, and allows the future improvement from both detailed steps and general scope.

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