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A pilot study for establishing quality indicators in molecular diagnostics according to the IFCC WG-LEPS initiative: preliminary findings in China

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Abstract

Background: Quality indicators (QIs) are crucial tools in measuring the quality of laboratory services. Based on the general QIs of the Working Group "Laboratory Errors and Patient Safety (WG-LEPS)" of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), specific QIs have been established in order to monitor and improve the quality of molecular diagnostics, and to assess the detection level of associated disease.
Methods: A survey was conducted on 46 independent commercial laboratories in China, investigated using questionnaires and on-site inspections. Specific QIs established were mainly based on the specific laboratory workflow for molecular diagnoses. The specific QI results from three volunteer laboratories were collected and used to validate their effectiveness.
Results: Of the 46 laboratories participating in the study, 44 (95.7%), conducted molecular diagnostics. Of 13 specific established QIs, six were priority level 1, and seven, priority level 3. At pre-evaluation of data from the three volunteering laboratories, it was found that the newly classified specific QIs had outstanding advantages in error identification and risk reduction.
Conclusions: Novel specific QIs, a promising tool for monitoring and improving upon the total testing process in molecular diagnostics, can effectively contribute to ensuring patient safety.

Keywords: error; molecular diagnostics; quality improvement; quality indicators; total testing process.

Introduction

The total testing process (TTP), starting from test request and ending with result interpretation, can be divided into three phases: pre-, intra- and post-analytical [1]. Errors in the TTP directly affect the accuracy of test results [2] and, as statistically demonstrated, the error-generating frequency is different at each stage of the TTP [3]. A body of evidence has been accumulated on the relevance of the extra-analytical phases, namely the pre-analytical steps, their vulnerability and impact on the overall quality of the laboratory information [4]. Due to the use of the universal promotion of quality assurance tools and quality assurance programs, the percentage of error in the TTP are significantly reduced [5].

Quality indicators (QIs) comprise a quality assurance tool, enabling users to measure the quality of laboratory services and represent a promising strategy for collecting data on quality in the TTP and, thus providing useful information for quality improvement projects and risk reduction [6, 7]. Moreover, documents issued by the International Organization for Standardization (ISO), the Clinical and Laboratory Standards Institute (CLSI) and the College of American Pathologists (CAP) also require laboratories to establish and monitor their own QIs [8–10]. Therefore, the establishment and application of QIs covering the TTP should be considered "a must" for complying with the requirements of the International Standard and achieving accreditation. Currently, international and regional organizations have established related QIs. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group "Laboratory Errors and Patient Safety" (WG-LEPS) has developed a Model of Quality Indicators (MQI), available on www.ifccmqi.com, which is used for collecting data from laboratories at an international level [11]. The group constantly updates the inventory of the QI and reporting system, and finally optimizes the MQI including the key process, the support process and result measurement. Moreover, a priority hierarchy, has been assigned to each indicator to facilitate

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the introduction of these QIs in the routine workflow of clinical laboratories [12]. Furthermore, with the number of participating laboratories increasing, quality specifications for QIs are established based on the data collected and are classified into three levels: optimum, desirable and minimum [13]. Except for the traditional expression of data in a percentage (%), the six sigma metric has been introduced as it is widely recognized as "a metric for measuring defects and improving quality" [14, 15].

With the emphasis on precision medicine (PM), accurate diagnosis and targeted precise treatment of diseases are carried out at the level of molecular diagnosis [16]. Molecular diagnostics have been widely applied in the life science and medical fields in recent years, contributing to the further enhancement of laboratory testing in clinical medical decision-making [17–21]. However, the test of molecular diagnostics is the most laboratory-developed tests (LDTs), which means molecular diagnostics has great flexibility and high risk [22]. This puts enormous pressure on the management, training and quality control of molecular diagnostic laboratories, including testing experiments and biological information analysis [23]. It is necessary to effectively identify preventive medical error, to implement risk management, and thus to improve the quality in diagnostic laboratories. QIs, as a well-designed quality management tool, have outstanding advantages in identifying and monitoring preventive medical errors and improving laboratory performance, and have been used in routine laboratories for many years. The introduction to molecular diagnostics is innovative to ensure experimental reliability and patient safety.

In view of these issues, the IFCC WG-LEPS aims to propose new specific QIs to monitor the activities inherent in molecular diagnostics, which can have an important impact on test results and patient outcomes. The present study reports on the established and pre-evaluated specific QIs used for monitoring analytical activities in molecular diagnostics by means of a questionnaire survey and peer consultation.

Materials and methods

Questionnaire survey

The questionnaire was designed in order to appraise the organizational context of the laboratories involved in the study. The organizational context included the discipline of the laboratory and specimen volume, etc. Forty-six independent commercial laboratories in China were recruited, and participants were asked to return completed questionnaires, distributed via e-mail (bccl_org@163.com), to the official mailbox of Beijing Center of Clinical Laboratory (BCCL) within a specific time frame. Figures 1 and 2 list the main contents and results of the questionnaire survey.

The results of the laboratory questionnaire surveys were summarized, and on-site inspections arranged accordingly. The aim of the on-site inspection was to identify how independent commercial laboratories affected the quality of the molecular diagnoses provided.

Establishment and pre-evaluation of specific QIs in molecular diagnostics

Phase 1: The literature review: According to the "WG-LEPS" prework basis and related consensus published, we summarized existing QIs and quality specifications.

Phase 2: Peer discussion: A discussion group meeting (consisting of 58 individuals) was held during the autumn of 2017. Participants included clinical physicians, pathologists, senior technologists, bioinformatics analysts, genetic counselors, laboratory managers, information technology personnel, research and development personnel, clients, etc. Minutes were taken and summaries were shared with all the participants. The participants agreed with that the existing QIs in pre-analytical phase but did not agree with the existing intra QIs due to issues on the applicability in molecular diagnostics. Therefore, it was necessary to establish specific QIs. Participants put forward new opinions, and finally, a total of 22 candidate QIs were distilled from the collation of the meetings.

Two discussion expert group meetings (consisting of 12 and 10 individuals, respectively) were held during the spring of 2018. The QI list mentioned was edited to remove the ambiguous QIs and to merge the duplicate QIs. A final list including 13 QIs were approved by peer consultation (see Tables 1 and 2).

Phase 3: Pre-evaluation of the specific QIs in molecular diagnostics: Three molecular diagnostic laboratories were recruited and the data on the specific QIs was collected for every month of the year of 2017

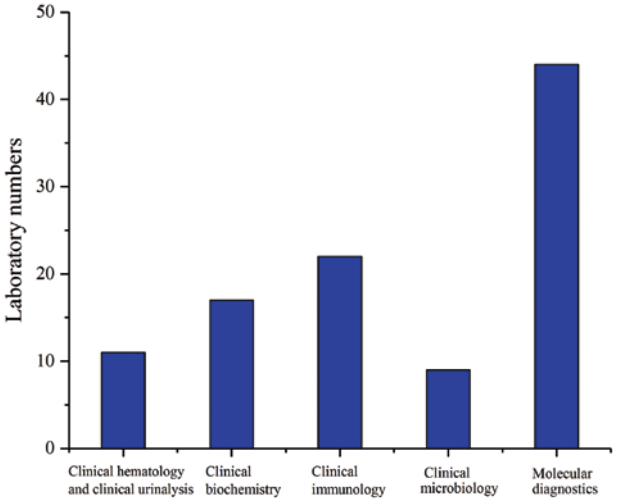

Figure 1: Distribution of different disciplines in 46 independent commercial laboratories.

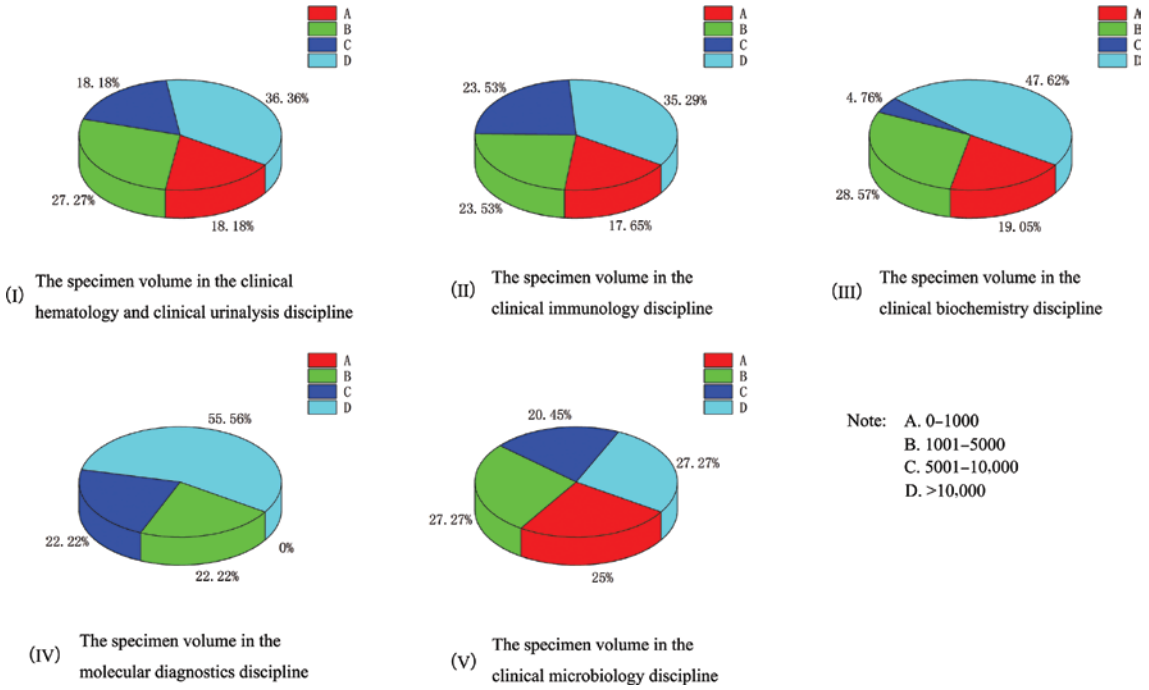

Figure 2: The specimen volume of each discipline in 46 independent commercial laboratories.

in order to evaluate the QIs on the effect of quality improvement in molecular diagnostics. The percent rate was calculated.

Results

Questionnaire survey

All of the 46 distributed questionnaires were duly completed and returned (recovery rate, 100%). Moreover, while 95.7% of laboratories performed molecular diagnostics, routine clinical biochemistry was performed only in 37%, and clinical hematology and urine analysis in 23.9% of laboratories. The number of laboratories engaged in molecular diagnostics increased significantly in recent years. The specimen volume of the molecular diagnostics discipline accounted for a large proportion of the business of independent commercial laboratories (see Figures 1 and 2).

The majority of independent commercial laboratories surveyed were engaged in the provision of molecular diagnostics. Molecular diagnostics had the following characteristics: (1) stringent hardware requirements, explicit experimental partition, and the unidirectional airflow which must be ensured to avoid cross-contamination. (2) High personnel requirements, such as pathologists and genetic analysts. (3) Long testing cycles, and there were many quality control points in the TTP. The next-generation sequencing (NGS) was the mainstream technology used in independent commercial laboratories, the work scheme of the TTP is illustrated in Figure 3. The prolonged time required explained the high frequency of errors in molecular diagnostics. Moreover, the majority of the tests carried out by molecular diagnostic laboratories were mostly LDTs, and there was a lack of external quality assessment (EQA) programs conducted by third-party authorities. To ensure the accuracy of test results, errors in the molecular diagnostics procedure must be monitored, especially during the analytical phase.

Establishment and pre-evaluation of specific QIs

Establishment specific QIs of molecular diagnostics

Based on the results of questionnaire survey and peer consensus, specific QIs were introduced to improve the quality in diagnostic laboratories. Furthermore, NGS is the mainstream technology for molecular diagnostics. The QIs covered the key activities of NGS, including “Unsuccessful DNA extraction rate”, “Unsuccessful library rate”, “Unsuccessful sequencing rate” and “Unsuccessful data analytical rate”. Those were process indicators, with a priority level 1 (mandatory) according to IFCC WG-LEPS empirical,

Table 1: Priority level 1 (mandatory) QIs presenting the key links for laboratories conducting molecular diagnostics.

Key processes **Specific quality indicators – Priority 1**					
Quality indicator	**Code**	**Calculation formula**	**Data collection**	**Frequency**	**Explanatory note**
Intra-analytical					
Unsuccessful DNA extraction rate	Intra-DNA Ext	Percentage of: number of one time unsuccessfully extracted samples/ total number of extracted samples	a) Count number of one time unsuccessfully extracted samples; b) count total number of extracted samples; c) calculate percentage	Data collection: every day Input data: monthly	Evaluation of successful DNA extraction coverage: (a) total DNA; (b) DNA fragment size; (c) DNA purity
Unsuccessful library rate	Intra-Lib	Percentage of: number of one time libraries do not pass QC/total number of libraries	a) Count number of one time libraries do not pass QC; b) count total number of libraries; c) calculate percentage	Data collection: every day Input data: monthly	Evaluation of successful library coverage: (a) total library yield; (b) library fragment size
Unsuccessful sequencing rate	Intra-Seq	Percentage of: number of unsuccessful runs for one sequencing/ total number of runs for this model in a certain period of time	a) Count number of unsuccessful Runs for one sequencing; b) count total number of Runs for this model in a certain period of time; c) calculate percentage	Data collection: every week or month Input data: monthly	Evaluation of successful sequencing coverage: Q30
Unsuccessful date analysis rate	Intra-Dat	Percentage of: number of one time date analysis do not pass QC samples/ total number of analysis samples	a) Count number of one time date analysis do not pass QC samples; b) count total number of date analyzed samples; c) calculate percentage	Data collection: every week or month Input data: monthly	Evaluation of successful date analysis coverage: (a) pairing consistency; (b) mapping rate; (c) average sequencing depth of unique reads; (d) covering uniformity
Post-analytical					
Report error rate	Post-Err	Percentage of: number of rectified reports by laboratory after the release/ total number of released reports	a) Count number of rectified reports by laboratory after the release; b) count total number of released reports; c) calculate percentage	Data collection: every day Input data: monthly	Rectified reports include inappropriate/ missed interpretative comments or erroneous patient details
Report delay rate	Post-Del	Percentage of/ number of delayed reports/total number of reports	a) Count number of delayed reports; b) count total number of reports; c) calculate percentage	Data collection: every day Input data: monthly	Delayed reports = reports which exceed the TAT specified by laboratory TAT = from sample reception by laboratory to release of result

QI, quality indicator; TAT, turnaround time; QC, quality control.

which could be used to identify error sources and ensure the accuracy of results. In addition, the "Report error rate" and "Report delay rate", which were outcome indicators, could be used to evaluate the risk of error impacting on patient outcome. The description in detail was as followed.

1. Unsuccessful DNA extraction rate

This indicator was used to monitor the stability of DNA extraction in the laboratory. The formula was expressed by the number of one time unsuccessfully extracted samples/ total number of extracted samples at the periodical time. It was recommended to monitor the QI according to different test systems and different DNA types separately. For the evaluation criteria of the success of DNA extraction, it was recommended to focus on three aspects: (a) total DNA; (b) DNA fragment size; (c) DNA purity [24].

2. Unsuccessful library rate

This indicator was used to monitor the stability of the laboratory building. The formula was expressed by the number of unsuccessful libraries at one time/total number of libraries at the periodical time.

Table 2: Priority level 3 (advisory) QIs suitable for personalized cancer treatment.

Key processes
Specific quality indicators – Priority 3

Quality Indicator	Code	Calculation formula	Data collection	Frequency	Explanatory note
Positive rate of *EGFR* – lung cancer	Post-Rate-*EGFR*Lu	Percentage of: Number of samples with *EGFR* mutations typical of lung cancer/total number of samples showing lung cancer	a) Count the number of *EGFR* mutations of lung cancer samples before this time b) count the total number of lung cancer samples c) calculate percentage	Data collection: monthly Input data: monthly	Detection rate of *EGFR* gene in lung cancer
Positive rate of *BRAF* – melanoma	Post-Rate-*BRAF*Me	Percentage of: Number of samples with *BRAF* mutations typical of melanoma/total number of samples with melanoma	a) Count the number of *BRAF* mutations of melanoma samples before this time b) count the total number of melanoma samples c) calculate percentage	Data collection: monthly Input data: monthly	Detection rate of *BRAF* gene in melanoma
Positive rate of *KRAS* – colorectal cancer	Post-Rate-*KRAS*Clo	Percentage of: Number of samples with *KRAS* mutations of colorectal cancer/total number of samples with colorectal cancer	a) Count the number of *KRAS* mutations of colorectal cancer samples before this time b) count the total number of colorectal cancer samples c) calculate percentage	Data collection: onthly Input data: monthly	Detection rate of *KRAS* gene in colorectal cancer
Positive rate of *ALK* fusion-lung cancer	PosT-Rate-*ALK*Lun	Percentage of: Number of samples with *ALK* fusion of lung cancer/total number of samples showing lung cancer	a) Count the number of *ALK* mutations of lung cancer samples before this time; b) count the total number of lung cancer samples; c) calculate percentage.	Data collection: monthly Input data: monthly	Detection rate of *ALK* fusion gene in lung cancer
The positive rate of *ROS1* fusion – lung cancer	Post-rate-ROS1Lun	Percentage of: number of samples with *ROS1* fusion of lung cancer/total number of samples showing lung cancer	a) Count the number of *ROS1* mutations of lung cancer samples before this time b) count the total number of lung cancer samples; c) calculate percentage.	Data collection: monthly Input data: monthly	Detection rate of *ROS1* fusion gene in lung cancer
The positive rate of *IDH1/IDH2/TERT*-glioma	Post-*Rate-IDH/TERT*Gl	Percentage of: number of samples with *IDH1/IDH2/TERT* mutations of glioma/total number of samples showing glioma	a) Count the number of *IDH1/IDH2/TERT* mutations of glioma samples before this time; b) count the total number of glioma samples; c) calculate percentage	Data collection: monthly Input data: monthly	Detection rate of *IDH1*/*IDH2*/*TERT* gene in glioma
The positive rate of *Her2* amplification – breast cancer	Post-Rate-*Her2*Bre	Percentage of: number of samples with *Her2* mutations of breast cancer/total number of samples showing breast cancer	a) Count the number of *Her2* mutations of breast cancer samples before this time; b) count the total number of breast cancer samples; c) calculate percentage	Data collection: monthly Input data: monthly	Detection rate of *Her2* gene in breast cancer

QI, quality indicator; *EGFR*, epidermal growth factor receptor; *BRAF*, v-raf murine sarcoma viral oncogene homologue B1; *KRAS*, kirsten rat sarcoma viral oncogene homologue; *ALK*, anaplastic lymphoma kinase; *ROS1*, c-ros oncogene 1 receptor tyrosine kinase; *IDH1/IDH2/TERT*, Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) and telomerase reverse transcriptase (TERT); *Her2*, human epidermalgrowth factor receptor-2.

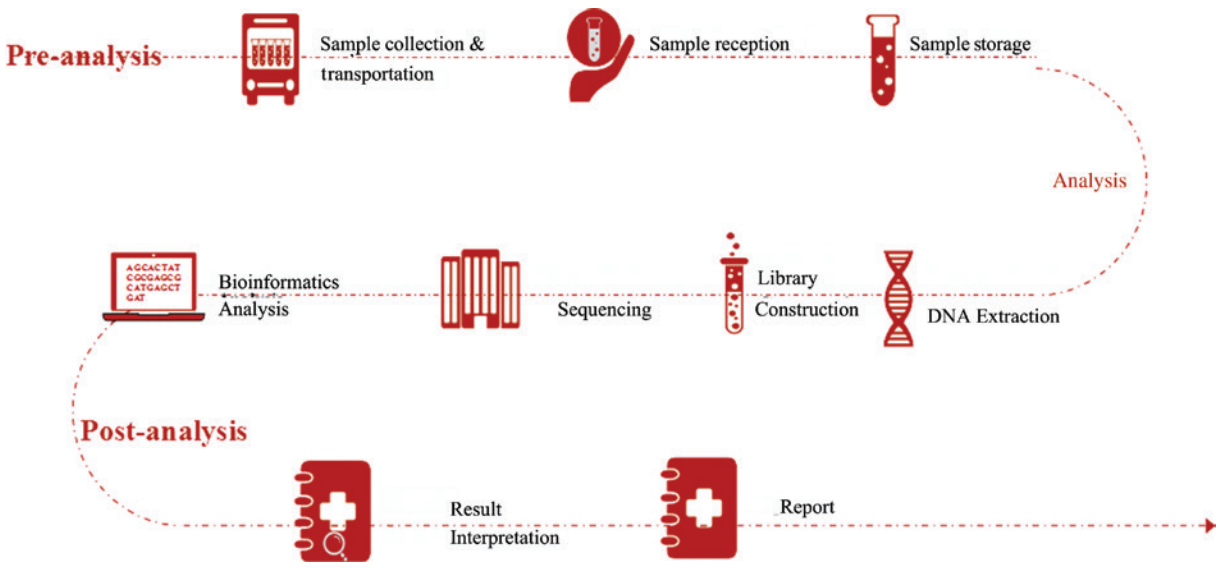

Figure 3: Workflow chart for TTP in molecular diagnostic laboratories.

To judge the success of a sample library, it was recommended to focus on two aspects: (a) total library yield and (b) library fragment size, which were subjected to DNA start amount, DNA quality, length after fragmentation, linker and index primer length, PCR amplification efficiency and the number of reactions [25].

3. Unsuccessful sequencing rate

This indicator was used to monitor the stability of the laboratory sequencer. The formula was expressed by the number of unsuccessful runs for one sequencing/total number of runs for this model at the periodical time. Differences existed in sequencing models. Taking the Illumina platform as an example, the indicator for determining the success or failure of sequencing was commonly used for Q30.

4. Unsuccessful data analytical rate

This indicator was used to monitor the stability of the laboratory test system. The formula was expressed by the number of one time date analysis that do not pass QC samples/total number of analysis samples at the periodical time.

To judge the success of data analysis, it was recommended to focus on four aspects: (a) Pairing consistency; (b) Mapping rate; (c) Average sequencing depth of unique reads; (d) Covering uniformity [26].

5. Report error rate

This indicator was the outcome QI. The formula was expressed by the number of rectified reports by a laboratory after the release/total number of released reports at the periodical time. The reporting errors mainly included two categories: basic patient information errors and test results errors.

6. Report delay rate

This indicator was the outcome QI. The formula was expressed by the number of delayed reports/total number of reports at the periodical time. The delayed reports referred to the reports which exceeded the turnaround time (TAT) specified by the laboratory. The TAT was equal to the time from sample reception by the laboratory to release of the result. The other information on six priority level 1 QIs is seen Table 1.

Except for the six priority level 1 QIs mentioned above, seven priority level 3 QIs, according to the IFCC WG-LEPS empirical, were established. They were the positive rates of the mutant genes, mainly used for measuring the detection level of the mutation associated with disease and was appropriate for personalized medicine for tumors. The positive rates of the mutant gene were evaluated by the comparison between cumulative single laboratory data, with the positive proportion of the population, to evaluate the laboratory testing performance [27, 28]. The specific QIs in molecular diagnostics are described in detail in Table 2.

Pre-evaluation the effectiveness of specific QIs

The effectiveness of the classified specific QIs in molecular diagnostics was pre-evaluated by three volunteer molecular diagnostic laboratories. For the QI of "Report delay rate", the 2017 annual data of the three laboratories are shown in Figure 4. Among them, the "Report delay rate" of Lab 2 in March was 11.4%, which was higher than the quality goal (7%, the median of the previous year's statistics) set by the laboratory. At the analysis, we found

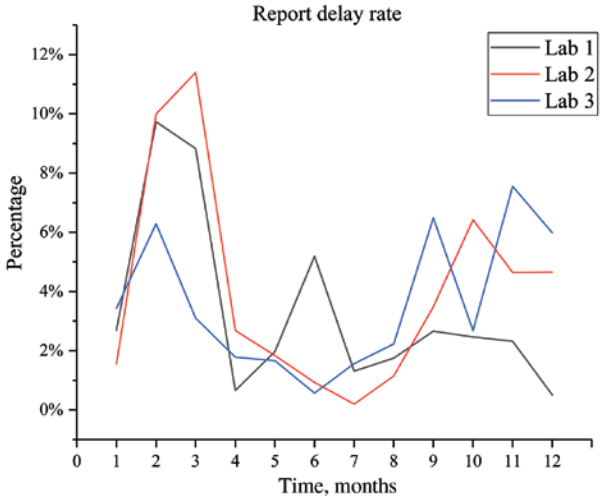

Figure 4: Statistics for the QI of "Report delay rate" in the three pre-evaluated laboratories by using the data in 2017.

that "TAT committed" in Lab 2's "Report delay rate" was defined as "natural day" instead of "working day", resulting in statistical errors rather than a laboratory quality inadequacy, which did not affect the accuracy of test results. The suggestions for improvement were that the laboratory should clearly define the procedure for data collection and data analysis to ensure the standardization of data collection and data statistics.

The statistics on the QIs of Lab 3's work process in 2017 is shown in Figure 5. Taking July as an example, the outcome indicator "Report delay rate" was 11.11%, which did not meet the quality goal (5%, of the median of the previous year's statistics) set by the laboratory. Further analysis of the process indicators during the same period revealed that the "Unsuccessful library rate" was only 44.44%, and the "Unsuccessful sequencing rate", 40%. This explains why the "Report delay rate" outcome indicator did not reach the quality goal. The suggestions for improvement included the training of related personnel, and the calibration of equipment for library construction and gene sequencing. The follow-up verification of August's data showed that when the process indicator "Unsuccessful library rate" was zero and the "Unsuccessful sequencing rate" was zero, the improvement was significant, and the "Report delay rate" was zero.

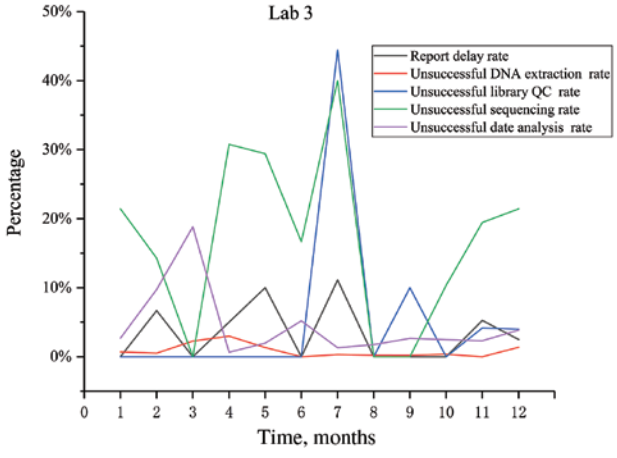

Figure 5: Statistics for the specific QIs in laboratory 3 by using the data in 2017.

Discussion

QIs are a quantified tool for monitoring errors, and measuring the degree to which intrinsic features meet requirements. At present, the WG-LEPS has established 27 QIs (21 concerning key processes; 3 support processes; 3 outcome measures) and the criteria required for defining quality specifications [13], based on the model defined at the landmark meeting held in Stockholm in 1999 [29] and the Milan Conference organized by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) [30].

In recent years, quality assurance for the pre-analytical (e.g. test requests, sample collection, processing and transportation) and the post-analytical (e.g. clinical feedback on laboratory results) phases through the use of QIs has become a research hotspot. Lippi et al. have reported on the use of QIs to improve quality by reducing the number of inappropriate specimens [31]; Zaninotto et al. on QIs to monitor time and temperature during transport of biological samples in order to guarantee the suitability of samples [32]; Piva et al. on QIs to assess the effectiveness of critical results communication and to monitor notification time in order to reduce the timeframe of clinical decision-making [33]. Likewise, although the errors in analytical phase have been significantly reduced thanks to the development and continuous use of internal quality control (IQC) and EQA over the past few decades [5], QIs have been proposed for monitoring the appropriateness of procedures undertaken.

However, with the application of LDTs and the advent of molecular diagnostics, the challenges faced by quality assurance in the analytical phase [34] call for the monitoring of errors in the analytical phase. The improvement of quality continues to be the "core business" of laboratory professionals and is still an unfinished journey [35]. Currently, molecular diagnostics with NGS is commonly used

in prenatal diagnostics, hereditary tumor testing, single-gene disease testing and pathogen testing, and these techniques play an increasingly important role in the effective prevention, diagnosis and treatment of diseases [36–38]. On the one hand, the process of molecular diagnostics is highly complex, and the reporting cycle relatively long [39] given that the analytical process involves nucleic acid extraction, library construction, gene sequencing, bioinformatics analysis, data interpretation and generation of test reports. On the other hand, molecular diagnostics currently lacks a unified IQC and EQA plan, and the existing QIs model established by the WG-LEPS is not entirely applicable to the quality monitoring of molecular diagnosis [26]. Therefore, the establishment of specific QIs, applicable to molecular diagnostics, can help laboratories to continuously monitor the errors in this type of testing, ensuring accurate results.

Specific QIs based on the preliminary experiences in combination with the specific workflow of laboratories and the suggestions of peer experts, are proposed. For each indicator, according to the criteria set by the WG-LEPS, a priority level has been defined in order to facilitate their introduction in clinical practice. Long-term external monitoring of the QIs are able to (a) allow you to measure your laboratory's performance against participating laboratories to help you set performance goals; (b) provide monthly reports to help you identify improvement opportunities and monitor the effectiveness of changes implemented over time; (c) establish benchmarks through external database comparisons.

These QIs also can be used for internal quality monitoring in order to improve the quality in the laboratory by comparison with related internal control criteria for each QI. Take "Unsuccessful DNA extraction rate" as an example, its internal control criteria mention (a) Total DNA: It is recommended that the minimum DNA input (LOD) is not lower than the performance of the laboratory test system; (b) DNA fragment size: DNA fragments with different degrees of degradation extracted by formalin-fixed paraffin-embedded (FFPE), it is recommended to define internal control standards by laboratory performance verification acceptable fragment size; plasma free DNA fragment main band is generally around 170 bp, more concentrated, and No significant large fragment contamination; (c) DNA purity: This index is applicable to whole genome DNA samples extracted from fresh tissues and blood cells. Generally, the total amount is high and the fragments are relatively intact and the quality is good. The DNA fragments are 20–40 kbp long and the DNA purity is generally A260/A280 is between 1.8 and 2.0, free of protein (aromatic) or phenolic substances [24].

This study is a preliminary work for the IFCC WG-LEPS. Now the established specific QIs are under maintenance on the official website of the IFCC WG-LEPS. In the future, we will collect the data from international laboratories for model validation and specification setup. A small number of laboratories and lack of data from international laboratories are the limitation of this phase study.

Conclusions

Molecular diagnostics is widely used in clinical practice and the NGS is the mainstream technology used. The establishment and use of specific QIs, allowing the continuous quality monitoring of laboratory processes for performance improvement in genetic diagnosis, can impact on test results and patient outcomes. In fact, the use of QIs in an inter-laboratory comparison enables the measurement of laboratory performance that can be compared with that of other participating laboratories, the identification of improvement opportunities and the monitoring of the effectiveness of changes implemented over time.

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