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Original Article

Quality Assurance Program for Molecular Medicine Laboratories

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Abstract

Background: Molecular diagnostic methods have played and continuing to have a critical role in clinical laboratories in recent years. Therefore, standardization is an evolutionary process that needs to be upgrade with increasing scientific knowledge, improvement of the instruments and techniques. The aim of this study was to design a quality assurance program in order to have similar conditions for all medical laboratories engaging with molecular tests.

Methods: We had to design a plan for all four elements; required space conditions, equipments, training, and basic guidelines. Necessary guidelines was prepared and confirmed by the launched specific committee at the Health Reference Laboratory.

Results: Several workshops were also held for medical laboratories directors and staffs, quality control manager of molecular companies, directors and nominees from universities. Accreditation of equipments and molecular material was followed parallel with rest of program. Now we are going to accredit medical laboratories and to evaluate the success of the program.

Conclusion: Accreditation of medical laboratory will be succeeding if its basic elements are provided in advance. Professional practice guidelines, holding training and performing accreditation the molecular materials and equipments ensured us that laboratories are aware of best practices, proper interpretation, limitations of techniques, and technical issues. Now, active external auditing can improve the applied laboratory conditions toward the defined standard level.

Keywords: Quality Assurance, Accreditation, Molecular Laboratory, Iran

Introduction

Nucleic acid amplification testing (NAT) in clinical specimens are increasingly used as a diagnostic tool in private clinical laboratories (1-3). These protocols are rapid and sensitive but needs to be standardized as a diagnostic method for patient's specimens (4-5). Therefore clinical validity remains controversial, until amplification tests to be proved reliable. At the present time laboratories are increasingly improving their instruments and space to apply molecular methods for diagnosis of bacterial, parasitic and especially viral agents that are highly claimed by the physicians (6-7). Molecular diagnostic methods are procedures that employing variety of technologies to help physician for better tailor patient treatments. A considerable number of these methods have been introduces to the clinical laboratory that needs to be standardized. Selecting a qualified instruments and running protocols at the diagnostic level are two most important facing problems especially in our country, because of their availability without any official permissions. These problems obviously cause on the sensitivity and specificity of the applied test (8). The most significant problems that must be solved before NATs to be become clinically useful; are false positive and false negative results (9).

Since introducing PCR, it has been developed and enhanced its quality of the performance the test for the clinical specimens. However, as a part of clinical service, a laboratory must maintain suitable quality in this area if accurate clinical information is to be provided to clinicians (10). Iran has a very widespread laboratory network. It is desired that this network, which has more than 4000 laboratories (public and private), achieve a certain level of quality, which is defined by national standards such as other country (11). This national reported standard has been based on the ISO 15189 and other specific issues regarding biosafety, management, external quality assessment, and so on (12,13).

Applying standard guidelines for the space, instrumentation, and sampling, shipping specimens and molecular diagnostic protocols is necessary to have similar results in all laboratories. It seems we are not able to consider those international regulations such as ISO 15189 for clinical laboratory, because they applied before setting up the required regulations. At this stage, we need to provide national measurements before obligating of all international laboratory criteria. Therefore, an independent quality assurance program based on our situations is required to be established specifically by the Health Reference Laboratories for monitoring molecular tests assays performed by those medical laboratories.

Methods

Development Quality Assurance program for the Molecular Methods

In view of the fact that there were no quality assurance program before (13), we have design specific program at first step based on the other country`s experiments (14). In this program we have to firstly publish all necessary guidelines and checklist, considering training especially for selected auditors and then accreditation. Therefore, an independent quality assurance program has been established specifically by the Health Reference Laboratories for monitoring molecular tests assays performed by those medical laboratories.

Standard Guidelines

Virology and Molecular Biology committee which established at 2008, in order to release some guidelines. The members of the committee participated in periodic benchmarking as a assessment of the laboratory performance in various provinces of Iran (15). They are going to be informed of applying running protocols and voluntary procedures or some probable deficiencies in the following provinces: Mazandaran, East Azarbayjan, Kermanshah, Sistan and Baluchestan, Kordestan, Gilan, Ghom, Fars, Esfahan, Kerman, Alborz and finally Tehran.

Training

In this regards various workshops were designed and held for all those auditors who introduced by Laboratory Affairs Offices of each province through the country**,** focusing in Tehran at first step. We considered some circumstances for this group such as having enough knowledge and experience in molecular methods, as well as no engaging with any molecular companies, and having reasonable attitude and habit.

Checklist

The next essential step was documenting an approved checklist in the field of molecular diagnosis tests. This check list had been prepared based on the released protocols. It was gradually modified in periodically benchmarking in some of provinces and finally was confirmed all modification and approved in the molecular biology committee. This checklist contained eighty one necessary questions on following items: personnel eligibility, bio-safety conditions, instruments qualifications, pre-analytical- analytical- and post-analytical processes, reporting sheet, and documentation of the results, storage conditions, quality of receiving and sending specimens, internal quality control program and finding error guidelines.

Accreditation program

It was decided to select 50 laboratories with the highest receiving samples per day in Tehran at the first accreditation program. Prepared checklist was

sent to all engaged laboratories with molecular tests to have self evaluation before attending our auditors at laboratories for molecular accreditation.

Results

Issued Protocols

Following guidelines were issued by the Virology and Molecular Biology Committee after several nonstop working (13):

1-Diagnostic molecular laboratory (especially for laboratory buildings and equipments), February 2008.

2- Implementation of bio-safety program in molecular laboratories based on ISO15190 and other references, January 2008.

3- Sampling, transportation and storage, July 2009.

4- Nucleic Acid extraction from pathogenic agents, summer 2009.

- Training: various workshops were held for the following groups: medical laboratories staffs, quality control officers of molecular companies, medical laboratory directors, directors and nominees from universities. Another workshop was also held regarding auditing.

- Molecular Companies Approving Process: All active companies in the fields of molecular providing materials must be accredited as well as molecular section of medical laboratories. All molecular companies are accredited by ISO13485. There are some accredited EQA providers based on ISO17043 who has not been prepared to be activated in molecular field yet. These companies asked to improve their condition under surveillance of Medical Equipments Office under the observation of Laboratory Technology Management Office of Health Reference Laboratory. All these companies are asked to be registered themselves and either those producing materials and kits or those who import from other abroad corporations in order to evaluate the quality of their molecular products. Considered registration process is as follows:

1- Complete the necessary forms regarding the activity fields

2-Introducing quality control officer

3-Confirmation of standard process of product or entrance and storage regulations

All those companies who are going to import material marked as "research use only" are not allowed to sell their materials and kits to the clinical laboratories. All provided materials are also classified according to their risk group. They are also asked to announce their Notified Body in abroad. Some materials may be sent to reference laboratory for evaluation their qualities after checking their documents. The products of all those qualified firms by Medical Equipments Office, are being introduced to the Medical Laboratories as a confirmed available products. At the present time 39 Iranian companies have been applied for registration that 30 ones have completed their process. Some products of just 8 companies have been qualified for importing.

Auditing of the clinical Laboratories

At this stage it has been decided to focus firstly on selected medical laboratory of Tehran since these laboratories are engaging with most other laboratories even from all provinces of Iran. Based on the bench marking experiment specially the analysis of Tehran that was the largest one (Table 1), we decided to have a pre-evaluation before any auditing.

Table 1: Analyzed data of Molecular Tehran Bench marking (%)

	Inspected Items	Frequency (%)
1	Dedicated Space	61.5
2	Provided Instruments	23
3	Storage conditions	77
4	Disposing the Swage	93
5	Extraction Procedures	83
6	SOPs for instruments	33
7	SOPs for protocols	77
8	Considered Correction Policies	30.7
9	Quality Control	7.7
10	Documentations of the tests	7.7
11	Documentations of Quality Control Experiments	7.7

Therefore a questionnaire was prepared and sent to the all laboratories regarding general question regarding the laboratories, current space and instruments, applied diagnostic protocols, quality assurance and control, and finally reporting. All collected information was analyzed (Table 2-5). The analysis results of the clinical laboratories at Tehran benchmarking are presents in table number one.

Table 2: Standardization of space and instruments according to guideline 1

	Asked question and subject	Frequency (%)
1	Current provided space	94
2	Applied necessary instruments	100
3	Documentations	100
4	Disposing the waste	100
5	Provided required bio-safety level	100

Table 3: Applied protocols for molecular diagnosis

	Asked question and subject	Frequency (%)
1	Applied imported extraction kits	76
2	Availability of alternative extraction protocols	84
3	Applied approved diagnostic protocols	64
4	Availability of alternative diagnostic protocols	87.5
5	Applied internal Control	100
6	Having policy use of CE-IVD, FDA	100

Table 4: Quality Assurance program

	Asked question and subject	Frequency (%)
1	Quality control of applied material before use	83
2	Use of reference materials	91
3	Use of independent freezer for molecular tests	91
4	Regular calibration of instruments	100
5	Regular calibration of termocyclers	96
6	Regular calibration of micropipette	100
7	Policy of confirmation results	
	Repeating the test on the original specimens	32
		29
	Repeating the test on the new specimens	13
		13
	Repeating the test with alternative protocols	
	Sending to other laboratory	
8	Intending to participate in external quality assurance program	95

Table 5: Required parameters on the reporting sheet

	Asked question and subject	Frequency (%)
1	Mention required parameters on the reporting sheet	
	Sensitivity	33
	Specificity	21.5
	Detection Limit	18.5
2	Specifying home brew protocol if using	13
3	Mention approved the diagnostic kit in the case of using	45
4	Keeping all necessary documentation of patient`s tests	100

Discussion

The primary goal of Laboratory Medicine is to provide information that is useful to assist medical decision-making, allowing optimal health care. Molecular testing is expanding rapidly in many areas, particularly in microbiology and virology within the current space in Iran`s medical laboratories. Clinical validation of the correctly calibrated routine conditions of molecular methods will take place, as soon as a reference measurement system is introduced and applied (16,17) In this regards we requires a clear definition of the clinically justifiable error of measurements and validation criteria for analytical performance (18). Therefore, performance and applying standardization is required for

improvement of results in Laboratory Medicine. Analysis of the questionnaire revealed all laboratories believed have collected all necessary instruments while bench marking showed only 23% of the laboratories had provided all required equipments. Documentations, and quality control policy also showed high differences between analyzed questionnaire and Tehran bench marking`s results. It means in the auditing this item must be carefully evaluated (Table 1, 2, and 4). Issued molecular guidelines with essential and minimal conditions and also approved checklist were the primarily goals at this stage. In order to achieve this standardization a confirmed approach is then needed, including approved space and instruments, appropriated reference procedures and materials, having required quality control program, applying confirmed molecular materials and kits as well as training. Regarding the minimal required standard space conditions, separation of pre-amplification area from post-amplification necessitated in this diagnostic field. Separation of positive and negative air pressure can help the staff for the applied policy and it allows them to use generic instrumentation for multiple assays efficiently. Another point is applied conditions for sample preparation area, because of sample-to-sample contamination especially in those laboratories with large preparation rate. A dedicated space must be in a format to allow the laboratory for contamination control. Besides the required standard space and approved materials and equipments our major challenge is applied quality control program of the running diagnostic tests and documentations, since all of them must be considered for validity and the reliability of the molecular results (19). These two recent parameters will be improving by the active auditing. Therefore, issuing specific checklist and self auditing of each laboratory will ensure us of taken similar policy. We hope at the first stage of auditing to enhance quality of the applied materials, setting up the necessity documentation, and ensuring of taken plan for the reliability of the tests.

Designed Quality assurance for the medical molecular laboratories will be evaluated by the regular and active auditing.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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The authors declare that there is no conflict of interest.

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