Journal of Ecohumanism
2024
Volume: 3, No: 8, pp. 12799 – 12809
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6091

The Role of External Quality Assessments in Clinical Laboratories: Review of Their Impact on Diagnostic Accuracy and Laboratory Performance in Molecular Pathology

Esam Abdullah Mohammed Abdullah Alaamri[1], Mustafa Ahmed Edrees Hamzi[2], Hafid Ahmed Mohammed Baydi[3], Yasir Ibrahim Yahya Kariri[4], Hassan Mohammed Ghabesh Ayashi[5], Aqdi Ahmed Saleh Y[6], Waseem Mohammed Hadidi Majari[7], Yasir Afandi Hamed Hakami[8], Majid Ahmed Abduh Refaei[9], Mohammed Ali Qasem Otayfi[10]

Abstract

External quality assessment (EQA) programs play a critical role in ensuring the accuracy and reliability of laboratory testing, particularly in the field of molecular pathology. Given the rising complexity of diagnostic tests and treatments for diseases such as cancer, robust EQA systems are essential for maintaining high standards of laboratory performance.This review examines the various types of EQA schemes implemented across clinical laboratories, focusing on their design, objectives, and impact on diagnostic accuracy. A comprehensive literature search was conducted across multiple databases, including MEDLINE, EMBASE, and CINAHL, to gather relevant studies and reports on EQA programs up to 2023.The review identifies several key findings: EQA programs significantly enhance laboratory performance by providing feedback that helps identify errors and areas for improvement. Diverse EQA schemes are tailored to different biomarkers and testing methodologies, emphasizing the importance of continuous education and training for laboratory personnel. Notably, participation in EQA programs has been associated with improved diagnostic accuracy and patient safety, particularly in oncology settings.EQA programs are indispensable for the advancement of laboratory quality assurance and the enhancement of patient care. They not only facilitate compliance with regulatory standards but also foster a culture of continuous improvement within laboratories. Future research should focus on optimizing EQA methodologies and exploring the integration of novel diagnostic technologies to further enhance laboratory performance.

Keywords: *External Quality Assessment, Molecular Pathology, Laboratory Performance, Diagnostic Accuracy, Patient Safety.*

Introduction

A diverse array of advanced laboratory testing and treatments has recently been accessible to cancer patients. The former are often costly, resulting in elevated health care expenses and possible strain on the patient. Consequently, it is essential that these testing methodologies and modern therapies be used just in suitable circumstances. Laboratory biomarkers are essential for patient selection because of their screening, diagnostic, prognostic, and therapeutic significance. To ensure that a laboratory consistently delivers trustworthy and accurate test findings, a robust quality management system and quality control are important [1-3]. This includes routine participation in external quality assurance (EQA) programs. The World Health Organization (WHO) defines the latter as "a system for objectively assessing the laboratory's performance through an outside organization or facility" [4]. This review will concentrate on molecular

[1] Ksa, Ministry of Health, Abu Arish General Hospital
[2] Ksa, Ministry of Health, Abu Arish General Hospital.
[3] Ksa, Ministry of Health, Abu Arish General Hospital.
[4] Ksa, Ministry of Health, Abu Arish General Hospital.
[5] Ksa, Ministry of Health, Abu Arish General Hospital
[6] Ksa, Ministry of Health, Jazan Genral Hospital
[7] Ksa, Ministry of Health, Abu Arish General Hospital
[8] Ksa, Ministry of Health, Abu Arish General Hospital
[9] Ksa, Ministry of Health, Blood Bank Center Jizan
[10] Ksa, Ministry of Health, Sabia General Hospital

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pathology diagnostics. Nonetheless, EQA systems exist across other domains, and numerous same concepts are applicable.

External agencies, referred to as EQA providers, orchestrate and manage EQA schemes to enhance transparency among labs, in contrast to ring investigations or ring tests, which frequently occur internally among laboratories without the involvement of an impartial external entity [5]. The term proficiency testing (PT) is sometimes used synonymously with external quality assessment (EQA), despite minor variances. EQA prioritizes ongoing development and education, while PT focuses more on compliance with regulatory standards [6]. Differences exist among EQA suppliers. Certain entities are associated with universities and conduct research [7,8]. Other EQA providers are associated with national or regional accrediting organizations and fulfill a dual function of organizing EQA schemes and granting formal laboratory accreditation [9]. For others, the organization of EQA schemes becomes their primary business [10]. EQA/PT suppliers may get accreditation in accordance with the International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 17043 to verify compliance with international standards [6,11,12]. ISO/IEC 17025 and ISO 15189 advocate for testing and diagnostic labs to engage with ISO/IEC 17043-accredited EQA/PT companies [11-14].

The EQA process generally comprises several stages: sample shipping, testing and reporting, expert evaluation, and the appeal phase. Participation in EQA is one aspect, while learning and enhancing performance based on outcomes, individual mistakes, or those from other laboratories is another. Both labs and EQA providers may get insights from an EQA system. Participation in EQA enables labs to assess their performance over time and to benchmark it against that of their peers. Consequently, labs may evaluate the efficacy of their daily testing methodologies, whether laboratory-developed tests (LDTs) or commercially available kits. Furthermore, EQA has shown its value by facilitating partnerships with the EQA supplier to examine the use and efficacy of their kits. Prior EQA study has demonstrated that EQA involvement may expose deficiencies in testing methodologies, such as significant disparities across staining procedures [15,16]. Moreover, EQA schemes and ring studies have contributed to the formulation of best practice recommendations by identifying hazards and prevalent mistakes [17,18]. To enhance patient care, the significance of EQA schemes and the insights gained from them will be paramount, alongside a variety of novel testing methodologies.

Diverse Categories of EQA Schemes

EQAs may be conducted in several circumstances. EQAs are broadly relevant and should be extensively used to achieve optimal health care outcomes. A variety of biomarkers may be assessed for various illnesses using several methodologies, each with distinct benefits and limitations. Anaplastic Lymphoma Kinase (ALK) changes may be assessed using immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), genetic analysis at the DNA or RNA level, and circulating tumor DNA (ctDNA) studies [19,20].

The objective of the EQA system must be explicit and capable of achieving its aims via its organization. Recently, numerous EQA schemes have been established to address the urgent issue of testing for the existence of SARS-CoV-2 [21]. These EQA methods have a definite objective. Various sorts of testing were rapidly created and were crucial for individual health and worldwide public health. Hasselmann et al. conducted an initial pilot study for SARS-CoV-2 testing, demonstrating that IgG testing is more dependable than IgM testing. Ast et al. [22] determined through their quality evaluation that approved tests yield more accurate results than non-certified tests. Additionally, Buchta et al. indicated that targeting specific viral genes leads to more reliable outcomes in their research [21-23]. Three distinct questions were addressed in these EQA plans; therefore, they are structured to precisely target these issues. In the absence of external quality monitoring, these discrepancies might not have been identified as promptly. The objective of identifying the most effective assays for accurately detecting the virus was achieved.

This example pertains to a prevalent illness; yet, uncommon disorders are also subjected to testing. In these instances, the objective is not to expedite the development of novel tests; instead, External Quality Assessment (EQA) is crucial to ensure accurate diagnoses, facilitating the prompt initiation of appropriate therapy where feasible. The selection or "production" of testing specimens for such EQA techniques is

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more challenging due to the limited availability of genuine instances in substantial volumes. EQA systems seek to provide participants with samples that closely resemble real-life scenarios [24].

Due to the diverse settings and varying objectives associated with the same biomarker test, several kinds of External Quality Assessment (EQA) schemes exist, targeting the pre-analytical, analytical, and/or post-analytical stages of the testing process. Some prioritize accurate outcomes exclusively, others seek to enhance the technical execution of techniques, some concentrate on meticulous record-keeping by clarifying reports to guarantee comprehensive documentation, while others emphasize communication by striving to eliminate ambiguity in result interpretation and conclusions.

Aspects of the pre-clinical phase subject to testing, maybe by questionnaire, include sample dealing with, sample preservation, test sequencing according to case history, sample setup, mistake rates, sample rejection rates, and their reasons, among others [25]. Malentacchi et al. investigated the impact of pre-analytical techniques and circumstances on the integrity of genomic DNA in blood samples, revealing a large disparity in gene copy numbers and considerable heterogeneity in gDNA integrity among labs [26,27].

The analytical step is extensively researched and entails dispatching samples to the respondents and evaluating laboratory findings. The technical efficiency of staining may also be evaluated if the IHC staining slides are returned to the EQA vendor [16]. Diverse methodologies may be explored for the same biomarker, since each has distinct benefits and drawbacks [28]. EQA schemes concentrating on ALK may examine FISH techniques only, IHC methods and their interpretative implications, or a comprehensive approach including all methodologies, such as DNA/RNA screening [16,19,29,30].

Numerous guidelines, suggestions, and an ISO standard are established for the appropriate implementation of an EQA program. This part will concentrate on molecular pathology EQA systems and include field suggestions. The ISO/IEC 17043 standard is designed to be applicable to all types of EQA schemes. The criteria and suggestions are organized into five primary categories and analyzed by Dufraing et al., presenting a unified perspective from EQA providers alongside an international steering group [12]. Tembuyser et al. outline other best practices for diagnostic labs and EQA suppliers, in addition to the essential criteria for clear and thorough clinical reports [31].

Upon registration for an EQA scheme, the EQA provider must explicitly convey the goal, sample quantity, and timing, while assembling a certified team of healthcare and technological specialists [11,12,31]. Samples must be of high quality, pertinent to the scheme, and chosen by experts in the area recognized as competent by the EQA providers [11,12,31]. It is important to acknowledge that using genuine patient samples is not always feasible, and synthetic samples may not always represent reality, although efforts should be made to achieve this. Subsequently, participants must submit the required findings and/or return their samples. The specific feedback asked must be explicitly conveyed to the respondents [11]. The findings are evaluated by assessors in accordance with processes established prior to the commencement of the EQA system [11,12,31]. Ultimately, the participants will get their findings, reflecting the agreement reached by the assessors, which the participants may contest.

EQA providers may have certain obstacles when organizing their programs. Certain issues may affect the planning and organization of the EQA system. If there is no previous experience with EQA the company, it may be prudent to conduct internal audits to detect deficiencies in compliance with the ISO/IEC 17043 standard and pursue certification promptly [11]. An EQA program should be structured to closely replicate standard laboratory procedures. Samples must be meticulously chosen, which may be accomplished by collaborating with a community of recognized professionals. Tembuyser et al. have tackled several issues in this regard [31].

A further difficulty that exceeds the capabilities of EQA suppliers is the regular processing of samples. The objective is to evaluate the standard procedures of labs; nevertheless, EQA specimens are not consistently regarded as such. If participants fail to treat their samples like any other, it becomes a squandered opportunity, since the normal testing remains unexamined in such instances. The onus is on the participant,

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DOI: https://doi.org/10.62754/joe.v3i8.6091

and the EQA supplier can only stress that samples ought to be handled like regular samples to the greatest extent feasible.

An EQA provider accredited with ISO/IEC 17043 is equipped to evaluate potential risks and strategize to address issues that may arise during the implementation of an EQA system. ISO/IEC 17043 accreditation necessitates adequate staff training, explicit protocols for collaborator selection and sample choice for each EQA scheme, procedures for sample preparation and storage, assessment protocols concerning statistics, accurate outcomes and methodologies, and data analysis procedures [11]. In addition to these procedural processes, there are needs to follow communication protocols (e.g., providing explicit directions for respondents and establishing mechanisms for addressing concerns) and maintaining anonymity throughout the whole EQA process [11].

Categories of EQA Organizations and Programs

EQA providers are accountable for the establishment, coordination, and oversight of EQA programs. Various attributes distinguish various suppliers. Certain providers concentrate on a single EQA scheme, whilst others manage numerous EQA systems [32,33]. Numerous suppliers concentrate on national clinical labs, but others aim to engage a broader audience. Another significant characteristic is the ISO/IEC 17043 certification level of the EQA supplier.

ISO/IEC 17043 certification guarantees the proper organization and implementation of accredited EQA schemes, as well as the proficiency of the EQA supplier [11]. Certification of an EQA source for a specific EQA scheme does not imply that other EQA schemes offered by that organization are accredited. For every EQA program, a determination is made on its total inclusion within the audit scope. The EQA provider is assessed only on the EQA schemes within the defined scope, and only these schemes are eligible for accreditation. Moreover, ISO/IEC 17043 delineates broad prerequisites applicable to all forms of EQA schemes and establishes a foundation for more particular technological criteria that vary across various domains [11]. Examples of recommendations that elaborate on technical requirements based on ISO/IEC 17043 certification are those by Dequeker et al. for CFTR testing and Langerak et al. for suspected lymphoproliferations, respectively [34,35].

ISO/IEC 17043 certification is conferred by the national accrediting authority of the country in which the EQA service is located. Entities accredited with ISO/IEC 17043 by their national accrediting authority are enumerated on the respective accrediting body's website. Providers are not required to be certified to administer EQA programs. EQA schemes and EQA providers may possess distinct objectives. An EQA provider's objective may center on structuring schemes to ensure accurate test results in national reference laboratories, while another objective may involve targeting a broader population and investigating the methodologies employed globally and their comparative efficacy. The feedback for each objective of an EQA system may vary significantly for the participating laboratory [36]. Their target market consists only of Belgian clinical labs, and the feedback provided to these laboratories encompasses the accuracy of analytical outcomes and potential areas for improvement [37].

Another EQA service, CF Network, specializes on the Cystic Fibrosis Transmembrane Conductivity Regulator (CFTR) gene [32]. They aim to enhance the quality of diagnostic and conduct research on the longitudinal efficiency of DNA testing labs, the interpretation of test findings, and the presentation of results. The target population include all clinical diagnostic tests for CFTR mutations globally. To conduct studies, additional data is solicited from participants, and further input is provided at the conclusion of the EQA scheme, particularly about the reporting of identified mutations with varying effects [38]. A crucial component of an EQA program is the analysis of test outcomes. In molecular pathology, screening extends beyond mutation identification, since certain illnesses result from gene fusions or clonal growth of blood cells; therefore, EQA vendors also implement methods for these particular purposes [39-41].

The selection of samples is contingent upon the procedures to be evaluated in the EQA scheme; hence, EQA providers must exercise meticulous attention in their sample selection. An exemplary sample for an EQA system should accurately reflect real-life specimens with comparable minimum abundance, relevant

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variant allele frequencies, and conditions like to those often seen in hospital labs. Samples are sometimes prepared first to maximize preservation, with testing conducted thereafter on formalin-fixed, paraffin-embedded (FFPE) substance. Likewise, DNA may be retrieved from body fluids, using a tube containing the DNA for testing purposes. Both alternatives may be chosen by an EQA provider; however, the selection of sample format should be grounded in rationale.

If EQA suppliers concentrate on the diagnostic procedures specifically, distributing pre-extracted DNA ensures comparable DNA quality for analysis across labs. Nonetheless, a provider may choose to include the assessment of the extraction procedure inside the EQA system and dispatch FFPE samples from which labs must independently extract DNA. During the analysis of outcomes, these factors must be taken into account to facilitate comparison across participants. It is essential to consider the primary objective of the EQA providers during each phase of the EQA establishment.

Significance of External Quality Assessment Programs for Laboratories as well as Clinical Practice

The primary objective of EQA programs is to improve patient safety and care by identifying laboratory mistakes and highlighting opportunities for improvement in laboratory tests. EQA enables labs to track their progress continuously and to compare it with that of their peers. The criteria for marking used in the EQA evaluation must be explicitly documented and validated by the experts. ISO/IEC 17043 recommends the following measurements: overall performance relative to prior standards, inter- and intra-participant variance, variation across techniques or processes, instructional feedback and guidance, and general observations, among others [11]. Feedback acquired during EQA participation may be used by labs to implement corrective and preventive measures (CAPAs) in practice. Miller et al. categorized several issues that may arise during External Quality Assessment (EQA), such as clerical mistakes, methodological issues, equipment malfunctions, technical difficulties attributable to human mistakes, or complications related to the proficiency testing (PT) material [42].

The laboratory is obligated to enhance its practices proactively. Participants who disagree with their score or find some input unclear may file an appeal to seek more clarification about their conclusion or, in certain cases, request assistance with the setting up of CAPAs or enhancement initiatives in their laboratory. Furthermore, consistent participation in EQA schemes is mandatory for accreditation as a testing or medical laboratory in accordance with ISO/IEC 17025 or ISO 15189 [13,14]. In nations such as France, labs handling human specimens for diagnostic reasons must get ISO 15189 accreditation [13]. Prior retrospective research on external quality assurance in genetics and molecular pathology have shown enhanced laboratory performance among those who consistently engaged in EQA schemes, underscoring the educational significance of EQA [1,38,43-46]. Studies indicate that labs should initiate External Quality Assessment (EQA) promptly after the introduction of novel biomarkers. Nonetheless, we must recognize that, in addition to the educational component of EQA, other variables may influence these outcomes. Experience with the plan, involvement bias, and the growth of scheme structure may affect performance [47].

The Scientific Significance of EQA Programs and Their Importance for Industry

Besides evaluating individual laboratory performance, EQA schemes provide valuable insights that address scientific inquiries by comparing extensive data from global labs. EQA systems in molecular pathology have identified several significant mistakes across all stages of the testing procedure. Laboratories are often accountable for guaranteeing adequate training and the effective implementation of various analytical procedures. The degree and method of training for certain procedures might differ across labs and pathologists [45].

The samples delivered during EQA schemes must meet particular criteria for participants to get similar samples [11]. Nonetheless, the results of an analysis remain contingent upon the pathologist's interpretation. Chosen tumor specimens that are given possess a defined minimum quantity of tumor cells, and pathologists must appropriately interpret this proportion. However, significant variability in the assessment of tumor cell structure in tumor specimens has been revealed throughout the pre-analysis stage [48,49]. The

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impact of over- or under-estimations on test results necessitates harmonization. Training significantly contributes to the process [50]. To execute this, extensive data on these estimates is required to establish inter-observer concordances and identify bias-inducing elements in the testing procedure.

A comparison of three RING trials undertaken by the Tumor-Infiltrating Lymphocytes (TILs) Working Group evaluating stromal TILs scores (sTILs) has shown the primary problems and inaccuracies in this assessment. The intraclass correlation coefficients (ICC) of the three ring investigations varied from 0.70 to 0.89, affected by obstacles including inflammatory cells, tumor boundaries, and other variables [17]. Comparative analysis of these ring trials shown that discrepancies in TIL estimate may be mitigated by (1) supplying reference pictures with a predetermined TIL proportion for instance, and (2) assessing several tumor regions to circumvent intratumoral complexity and random mistakes [51].

Accreditation generally improves a laboratory's analytical performance, resulting in fewer analytical mistakes, inconsistent findings, and technical inaccuracies compared to non-accredited labs [45,52]. These findings illustrate the significance of EQA involvement in achieving optimal performance. As certification of medical labs is not mandatory in all countries, involvement in EQA programs is crucial for achieving acceptable test quality. Moreover, the introduction of a novel biomarker, together with certification and subsequent EQA participation, facilitates its rapid integration into standard clinical practice, perhaps linked to the implementation process [45,53].

Longitudinal findings from EQA strategies indicate that the adoption of an alternate anticipatory molecular assessment in a laboratory positively impacts false negatives or erroneous results; however, it also introduces additional technical failures, underscoring the necessity of proper training prior to routine implementation [54]. The immunohistochemical staining efficacy for various biomarkers, including Programmed Death Ligand-1 (PD-L1), ALK, and ROS1, exhibits variability in sample processing and has been shown to improve with multiple EQA participations, likely due to peer comparison and subsequent individual feedback post-EQA [16,55]. The use of industrial kits yields superior staining performance relative to LDTs [16,56]. However, a proven technique that ensures high staining quality is crucial for achieving an appropriate staining score, while also considering the interpretative skills of the pathologist to minimize inter-individual variability and prevent misclassification or misunderstanding [15,16,57,58]. Furthermore, certification positively influenced the staining efficiency and understanding of these biomarkers [55].

Post-analytically, the description of variants must be accurate and adhere to the principles established by the Human Genome Variation Society (HGVS) [59,60]. 2016 research by Tack et al. [58] analyzed findings from four distinct EQA sources to identify frequent variant naming problems. Problematic areas consisted of, among others, clerical inaccuracies, use of conventional terminology in lieu of HGVS nomenclature, and the exclusion of p. or c. [10, 41, 61]. Nevertheless, the delivery of comprehensive feedback has shown efficacy in enhancing performance during future engagements [62].

Research has shown that involvement in EQA programs is an effective mechanism for enhancing test quality in labs and provides individual feedback for improving interpretation and reporting. Furthermore, the evidence amassed in this domain has resulted in the formulation of instructions and suggestions to counsel medical laboratories regarding their involvement in external quality assurance initiatives and the stages of the testing process (such as marker analysis); comprehension and reports; HGNC recommendations; and HGVS recommendations [28,35,60,63-69].

Statistics from EQA schemes provide insights on the impact of certain forecasting methodologies. In 2020, research by Keppens et al. demonstrated that next-generation sequencing (NGS) and non-NGS commercial kits were more effective than in-house non-next-generation sequencing methods for accurately detecting supplementary EGFR c.2369C>T p.(Thr790Met) in non-small cell lung cancer (NSCLC) [50].

The identification of variations and the subsequent provision of targeted treatment is further hampered by the inconsistency in companion diagnostics, which permits funding for certain medications only when a designated diagnostic test is used, as shown by PD-L1 [70]. In this context, many papers indicated substantial discrepancies in the proportion of acceptable or accurate findings obtained by labs using LDTs

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compared to those in the U.S. Companion diagnostics authorized by the Food and Drug Administration (FDA-CDx) [71,72]. Consequently, the results of these research are crucial for assessing the efficacy of commercial kits or companion diagnostics (CDx), their appropriate use, and the need for updates to enhance sensitivity while incorporating certain uncommon variants.

Conclusions

The objective of EQA is to aid labs in evaluating testing effectiveness and to foster ongoing education. Diverse EQA systems exist for labs, each with distinct features and objectives. Laboratory science is a rapidly advancing discipline, necessitating EQA suppliers to adapt their schemes to include recent developments. Both labs and industrial research institutions may get significant advantages from analyzing the outcomes of EQA schemes. EQA providers must continuously adapt to their field and confront the problems they face to achieve their objectives.

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ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
https://ecohumanism.co.uk/joe/ecohumanism
DOI: https://doi.org/10.62754/joe.v3i8.6091

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Journal of Ecohumanism
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Volume: 3, No: 8, pp. 12799 – 12809
ISSN: 2752-6798 (Print) | ISSN 2752-6801 (Online)
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DOI: https://doi.org/10.62754/joe.v3i8.6091

دور التقييم الخارجي للجودة في المختبرات السريرية: مراجعة لتأثيره على دقة التشخيص وأداء المختبرات في علم الأمراض الجزيئي

الملخص

الخلفية :تلعب برامج التقييم الخارجي للجودة (EQA) دورًا حاسمًا في ضمان دقة وموثوقية الاختبارات المخبرية، وخاصة في مجال علم الأمراض الجزيئي. ومع ازدياد تعقيد الاختبارات التشخيصية والعلاجات لأمراض مثل السرطان، تصبح أنظمة التقييم الخارجي للجودة ضرورية للحفاظ على معايير أداء مختبرية عالية.
المنهجية :تستعرض هذه المراجعة الأنواع المختلفة لبرامج التقييم الخارجي للجودة التي تُطبق في المختبرات السريرية، مع التركيز على تصميمها وأهدافها وتأثيرها على دقة التشخيص. تم إجراء بحث شامل في عدة قواعد بيانات، بما في ذلك MEDLINE و EMBASEوCINAHL، لجمع الدراسات والتقارير ذات الصلة ببرامج التقييم الخارجي للجودة حتى عام 2023.

النتائج :تكشف المراجعة عن عدة نتائج رئيسية: تعزز برامج التقييم الخارجي للجودة أداء المختبرات بشكل كبير من خلال تقديم ملاحظات تساعد في تحديد الأخطاء والمجالات التي تحتاج إلى تحسين. تُصمم برامج التقييم لتتناسب مع مختلف المؤشرات الحيوية ومنهجيات الاختبار، مما يبرز أهمية التعليم والتدريب المستمر للعاملين في المختبرات. ومن الجدير بالذكر أن المشاركة في برامج التقييم الخارجي للجودة ارتبطت بتحسين دقة التشخيص وسلامة المرضى، خاصة في سياقات علاج الأورام.

الخلاصة :تعد برامج التقييم الخارجي للجودة لا غنى عنها لتعزيز ضمان الجودة في المختبرات وتحسين رعاية المرضى. فهي لا تقتصر على تعزيز الامتثال للمعايير التنظيمية فحسب، بل تساهم أيضًا في تعزيز ثقافة التحسين المستمر داخل المختبرات. يجب أن تركز الأبحاث المستقبلية على تحسين منهجيات التقييم الخارجي للجودة واستكشاف دمج التقنيات التشخيصية الحديثة لتعزيز أداء المختبرات بشكل أكبر.

الكلمات المفتاحية :التقييم الخارجي للجودة، علم الأمراض الجزيئي، أداء المختبرات، دقة التشخيص، سلامة المرضى.