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External quality assessment programs in cytogenomics in the Lombardy Region, Italy (2018-2024): performance and trends

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Abstract

Background. This study summarizes seven years (2018-2024) of external quality assessment (EQA) activities in cytogenomics conducted in the Lombardy Region, Italy, across four diagnostic sectors: chromosomal microarray (CGH/SNP-array), prenatal cytogenetics, postnatal cytogenetics, and oncohematology.

Methods. A descriptive analysis was performed of the regional EQA cycles, focusing on analytical concordance and on the type and evolution of non-conformities over time.

Results. Analytical concordance remained consistently high across all EQA cycles, with correct identification of the primary findings in CGH-array and constitutional cytogenetics. Early rounds were mainly characterized by incomplete reporting, International system for human cytogenomic nomenclature (ISCN) inaccuracies, limited interpretive content, and insufficient communication of methodological limitations, whereas more recent cycles showed progressive convergence toward national (SIGU) and international (ACMG/ClinGen, European) standards. In microarray (CGH/SNP-array) exercises, inter-laboratory variability shifted from basic interpretive and reporting deficiencies to more advanced issues of standardization in 2023-2024. Prenatal and postnatal cytogenetics showed progressive improvement in report structure, ISCN compliance, and methodological completeness. Oncohematology remained the most challenging area, with persistent variability in complex karyotype reconstruction despite improved metaphase adequacy and more complete ISCN reporting.

Conclusions. These findings support the role of regionally coordinated EQA schemes in promoting harmonization of cytogenomic practice, continuous quality improvement, and public health governance.

Key words

- cytogenomics
- external quality assessment
- cytogenetics
- chromosomal microarray
- oncohematology

INTRODUCTION

Cytogenomic diagnostics, including chromosomal microarray analysis, classical cytogenetics and cytogenetic investigation of hematologic malignancies, are essential components of constitutional and cancer genetics. Ensuring accuracy, reproducibility and harmonization across laboratories requires the implementation of external quality assessment (EQA) systems. International initiatives such as ACMG/ClinGen recommendations for constitutional copy number variation (CNV) interpretation [1], European guidelines for cytogenomic analysis [2], and long-standing UK NEQAS/GenQA and EMQN programs (see the GenQA/UK NEQAS and EMQN websites) have progressively shaped quality standards. In Italy, quality assurance in cytogenetics has a solid tradition. The pioneering national project on standardization and quality assurance led by the Istituto Superiore di Sanità laid the groundwork for coordinated external assessment in the early 2000s [3]. This effort subsequently evolved into the

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Italian EQA Programme, including the cytogenetics scheme, and documented substantial improvements in laboratory performance following the introduction of explicit poor-performance criteria [4]. These national findings align with international experience, including more recent EQA models for karyotype analysis such as that proposed by Weng *et al*. [5], and reinforce the role of EQA as a driver of laboratory harmonization. In this context, the Regional Coordination Center for Laboratory Medicine (CRCMedLab) established, in 2018, a structured EQA scheme dedicated to cytogenomic diagnostics, covering chromosomal microarray (CGH/SNP-array), prenatal cytogenetics, postnatal cytogenetics and oncohematology. The objective of this manuscript is to present a consolidated longitudinal analysis of seven years of activity (2018-2024), comparing early and recent performance and evaluating the evolution of laboratory compliance, analytical concordance for the primary findings and reporting quality in relation to national and international EQA schemes.

MATERIALS AND METHODS

Diagnostic areas and EQA design

The cytogenomics EQA program of the Lombardy Region covered four diagnostic areas: prenatal cytogenetics, postnatal cytogenetics, hemato-oncological cytogenetics (oncohematology), and CGH/SNP-array analysis. Between 2018 and 2024, the program was implemented continuously and included both prospective and retrospective exercises across the four diagnostic sectors. The number of participating laboratories by year and diagnostic area is summarized in *Table 1*. Across the study period, the mean number of participating laboratories was 16 for CGH/SNP-array, 21 for postnatal cytogenetics, 17 for prenatal cytogenetics, and 19 for oncohematology. The overall distribution of EQA cycles is reported in *Table 2*. Two main types of exercises were organized:

- prospective assessments: DNA samples were distributed to participating laboratories, which performed routine analyses according to their standard protocols and submitted complete reports;
- retrospective assessments: laboratories were asked to send a report of pathological cases previously diagnosed in their routine activity during the preceding semester, using anonymized clinical and laboratory data.

In the prospective approach, all laboratories received the same control material and were requested to perform array-based analyses exactly as in routine practice. In the retrospective approach, laboratories re-submitted reports and interpretations for real cases they had previously managed, allowing evaluation of reporting quality, adherence to guidelines and interpretive consistency. The cytogenomics EQA scheme was coordinated by CRCMedLab and involved all diagnostic laboratories in the Lombardy Region performing cytogenetic and cytogenomic analyses.

Data submission and evaluation

For both the prospective and retrospective approaches, laboratories submitted results through the CRCMedLab website (www.qualitalaboratorilombardia.it). For each exercise, the following elements were evaluated, where applicable:

- analytical performance (detection of the main chromosomal abnormality or CNV);
- karyotype reconstruction;
- ISCN nomenclature accuracy and completeness;
- diagnostic interpretation and genotype-phenotype correlation;
- structure and completeness of the written report, including clerical accuracy and methodological limitations.

After the first three experimental years of the regional EQA program, a structured, penalty-based scoring

Table 1
Number of participating laboratories by year and diagnostic area in the Lombardy (Italy), cytogenomics EQA program (2018-2024)

Diagnostic Area	2018	2019	2020	2021	2022	2023	2024
CGH/SNP-array	19	-	-	18	15	17	16
Postnatal cytogenetics	-	25	22	-	22	19	19
Prenatal cytogenetics	-	17	-	16	16	19	19
Hemato-oncological cytogenetics	-	-	20	20	21	17	15

EQA: external quality assessment; CGH/SNP-array: chromosomal microarray.

Table 2
Cytogenomics EQA cycles conducted in Lombardy, Italy (2018-2024)

Diagnostic area	2018	2019	2020	2021	2022	2023	2024	Total number of exercises
CGH/SNP-array	X(p)			X(p)	X(r)	X(p)	X(p)	5
Postnatal cytogenetics		X(r)	X(r)		X(r)	X(r)	X(r)	5
Prenatal cytogenetics		X(r)		X(r)	X(r)	X(r)	X(r)	5
Hemato-oncological cytogenetics			X(r)	X(r)	X(r)	X(r)	X(r)	5
Total	1	2	2	3	4	4	4	20

EQA: external quality assessment; p: prospective; r: retrospective.

system with a maximum score of 30 was introduced for exercises requiring formal report-based evaluation. Three domains were assessed, each with a maximum score of 10 points: analysis (genotyping/nomenclature), interpretation, and report structure/content. Scoring was penalty-based: each domain was initially assigned a score of 10, from which predefined penalties were subtracted according to the evaluation criteria. Severe errors were classified as unsatisfactory performance, whereas predefined minor and major deficiencies led to specific score deductions. The full scoring framework is summarized in *Table 3*.

Data analysis was descriptive in nature and aimed at summarizing laboratory performance across EQA cycles. Error frequencies, proportions, and score distributions were compared over time to identify performance trends across diagnostic sectors and across early versus recent exercises. No formal inferential statistical testing was performed, as the primary aim of the EQA program was quality monitoring and harmonization rather than hypothesis testing. Evaluation criteria were aligned with SIGU recommendations for cytogenetic and cytogenomic diagnosis (available from the SIGU website), ISCN nomenclature, and international recommendations

Table 3
Penalty-based scoring system used for formal report evaluation in the Lombardy (Italy) cytogenomics EQA program. Each category was assigned a maximum score of 10 points. Scoring was penalty-based, with predefined deductions applied according to the evaluation criteria. Severe errors were classified as unsatisfactory performance

Category	Evaluation criterion	Applicable scheme(s)	Penalty/ outcome
Analysis (genotyping/ nomenclature)	Severe error: expected result incorrectly identified, including missed or incorrect identification of the abnormality	All schemes	Unsatisfactory performance
	ISCN formula: minor error (e.g., spacing, incorrect use of symbols)	All schemes	-0.5
	ISCN formula: incomplete	All schemes	-0.5
	ISCN formula: incorrect (misleading with respect to the analytical result, causing interpretive problems)	All schemes	-2
	ISCN formula: absent	All schemes	-2
	Explanation of the ISCN formula understandable to non-experts: incomplete (e.g., missing description of genotypic sex, observed abnormality, type of imbalance/rearrangement, chromosomes or chromosome arms involved, or missing indication of normal/abnormal karyotype)	All schemes	-0.5
	Explanation of the ISCN formula understandable to non-experts: incorrect or absent	All schemes	-1
	Karyotype reconstruction: incorrect in one of the evaluated karyotypes	Prenatal, postnatal, oncohematology	-0.5
	Karyotype reconstruction: incorrect in more than one of the evaluated karyotypes	Prenatal, postnatal, oncohematology	-1
	Number of metaphases analyzed: inadequate but reported in the report	Prenatal, postnatal, oncohematology	-0.5
	Number of metaphases analyzed: inadequate and not reported in the report	Prenatal, postnatal, oncohematology	-1
	Banding resolution: inadequate but reported in the report	Prenatal, postnatal, oncohematology	-0.5
	Banding resolution: inadequate and not reported in the report	Prenatal, postnatal, oncohematology	-1
	Same item previously penalized in earlier EQA exercises	All schemes	-5
Interpretation	Severe error: interpretation incorrect (e.g., misleading interpretation) or absent	All schemes	Unsatisfactory performance
	Missing clinical indication/indication not reported	All schemes	-1
	Incorrect indication of reproductive risk for the patient and/or the couple	All schemes	-1
	Failure to recommend extension of testing to family members, where appropriate	All schemes	-1
	Suggestion to perform inappropriate genetic analyses	All schemes	-2
	Incomplete: lack of correlation with the diagnostic question	All schemes	-1
	Incomplete: lack of prognostic risk information (when applicable) or lack of recommendation for multidisciplinary consultation/oncohematology consultation	Oncohematology	-1
	Incomplete: lack of recommendation for further diagnostic work-up/no reference to additional ongoing investigations	Oncohematology	-1

Continues

Table 3
Continued

Category	Evaluation criterion	Applicable scheme(s)	Penalty/ outcome
	Incomplete: lack of indication of recurrent abnormality or lack of recommendation for multidisciplinary consultation/oncohematology consultation	Oncohematology	-1
	Failure to comply with applicable recommendations/guidelines	All schemes	-1
	Same item previously penalized in earlier EQA exercises	All schemes	-5
Report structure and content	Language/terminology inadequate and potentially misleading	All schemes	-0.25
	Confusing report template or lack of clear structure	All schemes	-0.25
	Missing date of sample collection	All schemes	-0.25
	Missing date of sample receipt	All schemes	-0.25
	Missing report date	All schemes	-0.25
	Missing identification of the requesting physician or institution	All schemes	-0.25
	Incomplete patient identification (missing name, surname, or date of birth, as provided by the referring center/accompanying form in prospective exercises)	All schemes	-0.25
	Incorrect patient identification (incorrect name, surname, or date of birth, as provided by the referring center/accompanying form in prospective exercises)	All schemes	-1
	Missing indication of sex (as provided by the referring center/accompanying form in prospective exercises)	All schemes	-0.5
	Missing sample identification code	All schemes	-0.25
	Missing specimen/material examined	All schemes	-0.25
	Missing identification of the analyst and/or signature of the laboratory director or delegated staff	All schemes	-0.25
	Missing page numbering (e.g., 1 of 1)	All schemes	-0.25
	Missing indication for testing/diagnostic suspicion/clinical information	All schemes	-1.5
	Turnaround time not respected	Prenatal, postnatal, oncohematology	-1
	Absence of method description	All schemes	-0.25
	Missing information on test limitations	All schemes	-0.25
	Information on test technique insufficient or incorrect (e.g., sequenced region and/or mutation investigated and/or kit used)	All schemes	-0.5
	Analytical sensitivity and specificity absent or insufficient	All schemes	-0.5
	Same item previously penalized in earlier EQA exercises	All schemes	-5

EQA: external quality assessment; ISCN: International system for human cytogenomic nomenclature.

for CNV interpretation [1]. Final reports of each EQA exercise were made available on the CRCMedLab website (www.qualitalaboratorilombardia.it) within twenty working days after the program deadline.

RESULTS

CGH/SNP-array analysis

As shown in *Table 1*, participation in the CGH/SNP-array scheme ranged from 15 to 19 laboratories across active cycles. One case was distributed in each CGH/SNP-array EQA cycle, for a total of five cases across the study period. All distributed cases involved clinically relevant CNVs; no borderline CNVs were included. Across the five CGH/SNP-array EQA cycles, analytical concordance remained consistently high, with correct identification of the primary pathogenic copy-number variant in all exercises. However, the earliest array-based rounds showed substantial heterogeneity in interpretive and reporting quality. In 2018, although no laboratory failed to identify the clinically relevant abnormality, interpretation was fully correct in only 2/19 laboratories (10.5%), whereas 14/19 (73.7%) were judged correct with observations and 3/19 (15.8%) were classified as incorrect. Report content showed observations in all submissions (19/19, 100%), and omission of methodological limitations was also recorded in all reports. The most frequent deficiencies concerned omission of key analytical limitations, incomplete syndrome/OMIM reporting, and insufficient integration between genomic findings and clinical interpretation. By 2023, the profile had become more structured, with 17 laboratories evaluated and a mean score of 27.632/30. At this stage, evaluator comments were focused less on basic interpretive omissions and more on standardization issues, including use of the hg38 genome build, explicit indication of OMIM references, parental testing recommendations in terminal deletions, and clearer definition of CNV classification

criteria and methodological limitations. A further improvement was observed in 2024, when 16 laboratories were evaluated with a mean score of 28.945/30. In this round, residual comments were mainly limited to refinement of reporting practice, such as more explicit citation of interpretive guidelines, clearer indication of the number of genes involved in large CNVs, and improved consolidation of methodological characteristics and analytical limitations. Overall, these findings indicate that inter-laboratory variability progressively shifted from substantial interpretive and reporting deficiencies toward more advanced issues of report harmonization and standardization.

Hemato-oncological diagnostics (oncohematology)

As shown in *Table 1*, participation in the oncohematology scheme ranged from 15 to 21 laboratories across active cycles. Oncohematology showed the highest variability among the diagnostic sectors. The earliest evaluations identified recurring issues including inadequate metaphase numbers, incomplete description of clonal evolution, and errors in karyotype reconstruction. Quantitative comparison between 2020 and 2023 is reported in *Table 4*. Karyotype reconstruction errors increased from 2/20 (10%) in 2020 to 6/17 (35%) in 2023. Over the same period, inadequate metaphase number decreased from 6/20 (30%) to 2/17 (11.8%). ISCN syntax errors remained substantial, accounting for 7/20 cases (35%) in 2020 and 6/17 (35.3%) in 2023, whereas missing ISCN reports decreased from 2/20 (10%) to 0/17 (0%). Overall, these findings indicate improved adequacy of metaphase analysis and more complete ISCN reporting, together with persistent variability in the handling of complex karyotypes.

Table 4
Comparison of oncohematology EQA performance (2020 *vs* 2023)

Parameter	2020	2023
Participating laboratories	20	17
Karyotype reconstruction errors	2/20 (10%)	6/17 (35%)
Inadequate metaphase number	6/20 (30%)	2/17 (11.8%)
ISCN syntax errors	7/20 (35%)	6/17 (35.3%)
Missing ISCN reports	2/20 (10%)	0/17 (0%)
Mean total score	n/a	25.42/30

EQA: external quality assessment; ISCN: International system for human cytogenomic nomenclature; n/a: not applicable.

Table 5
Comparison of prenatal EQA performance (2019 *vs* 2024)

Parameter	2019	2024
Participating laboratories	17	19
Correct overall evaluation	16/17 (94%)	19/19 (100%)
Incorrect ISCN	1/17 (6%)	0/19 (0%)
Mean total score	n/a	29.61/30
Completeness of key elements	Variable	Near-complete

EQA: external quality assessment; ISCN: International system for human cytogenomic nomenclature; n/a: not applicable.

Prenatal diagnostics

As shown in *Table 1*, participation in the prenatal diagnostics scheme ranged from 16 to 19 laboratories across active cycles. The first prenatal EQA exercise, conducted in 2019, showed a generally good level of analytical performance, with 94% of centers providing a correct overall evaluation. However, a detailed review of the submitted reports highlighted several recurrent deficiencies, particularly in sections describing the analytical process. Missing or inconsistently reported elements included the culture method employed, the number of metaphases analyzed, the recommendation for genetic counseling and the unexpanded acronyms. These gaps reflected the heterogeneity of reporting practices before the introduction of updated national guidelines. A marked improvement emerged in the 2024 cycle, which included 19 participating laboratories. In this round, all laboratories achieved a correct analytical result (100%), and the mean total score reached 29.61/30, indicating a high level of adherence to expected standards. Reporting was generally complete and aligned with the updated SIGU recommendations, with almost all laboratories providing thorough methodological descriptions, complete ISCN notation and clearly structured reports. This evolution is summarized in *Table 5*, which illustrates the progression from heterogeneous and partially incomplete reporting in 2019 to a more standardized and comprehensive approach in 2024.

Postnatal diagnostics

As shown in *Table 1*, participation in the postnatal diagnostics scheme ranged from 19 to 25 laboratories across active cycles. Postnatal cytogenetics EQA exercises conducted between 2019 and 2024 demonstrated consistently high analytical concordance, with all participating laboratories correctly identifying the main chromosomal abnormality in each evaluation. However, qualitative review of submitted reports revealed recurrent deficiencies, particularly in the earlier cycles (2019-2021). The most frequent issues concerned administrative inaccuracies, unexpanded acronyms, heterogeneous methodological descriptions, and outdated ISCN terminology. In some reports, the postnatal origin of the analyzed karyotype was not explicitly stated, potentially generating ambiguity in clinical interpretation.

Because postnatal EQA assessments were primarily based on qualitative review of full written reports, numerical frequencies for each specific reporting deficiency were not available for all cycles. Nevertheless, assessor reports consistently documented progressive improvement over time. In the most recent cycles (2023-2024), report structure became more standardized, documentation of analytical methods improved, and interpretive comments were more complete and clinically relevant.

DISCUSSION

The Lombardy Regional EQA program demonstrates consistently strong analytical performance across all cytogenomic fields, a trend that mirrors both Italian national experiences and international comparison initiatives. In CGH/SNP-array analysis, analytical concor-

dance remained uniformly high throughout all cycles, consistent with findings from major international EQA schemes such as EMQN and GenQA (see the corresponding program websites) as well as Australasian microarray programs [6], where technical sensitivity is excellent while interpretive variability is the predominant issue.

The CGH/SNP-array scheme showed a clear temporal shift in the nature of non-conformities. In the earliest round, variability was driven mainly by incomplete interpretive content and omission of methodological limitations, despite correct identification of the primary genomic imbalance. By contrast, the later rounds showed a more mature reporting profile, in which the main residual issues concerned harmonization of terminology, use of updated genome builds, explicit reference to interpretive guidelines, and more structured integration of genomic and clinical information. In this context, the 2024 round can be regarded as the most standardized among the evaluated array cycles, not because a formal statistical ranking was applied across all historical rounds, but because evaluator comments were largely restricted to refinement-level issues and the mean score was higher than in 2023. The improvements observed in Lombardy – particularly in ISCN accuracy, structured reporting, and adherence to ACMG/ClinGen and European cytogenomic guidelines [1, 2], as well as updated SIGU recommendations (available from the SIGU website) – reflect broader trends toward harmonization in cytogenomic practice.

The Italian experience provides an important historical framework for interpreting these results. Early national quality-assurance initiatives, such as the Italian Project on Standardization and Quality Assurance led by the Istituto Superiore di Sanità [3], demonstrated the impact of structured evaluation in reducing inter-laboratory variability. Subsequent national EQA activities, including the Italian External Quality Assessment scheme in classical cytogenetics and the National Cytogenetics EQA Program (2013-2016), confirmed that explicit performance criteria and standardized reporting frameworks were effective in improving banding documentation, metaphase selection and ISCN accuracy [4, 7]. The Lombardy dataset reproduces these observations locally: analytical concordance remains high in all sectors, whereas the most frequent non-conformities involve ISCN nomenclature, incomplete documentation of methodological limitations and variability in interpretive content. The regional scheme also adds value by systematically evaluating CGH/SNP-array performance – an aspect only partially addressed in national cytogenetics programs.

In prenatal and postnatal cytogenetics, the progressive standardization observed in Lombardy paralleled both Italian and broader European experience. Early cycles were characterized by variability in administrative completeness, ISCN formatting, and documentation of analytical methods, whereas later evaluations, particularly after publication of the updated SIGU recommendations in 2023, showed clearer report structure, improved methodological documentation, and more consistent interpretive comments. These findings support the view that sustained EQA participation contributes not only to maintenance of analytical concordance, but also to harmonization of report quality and adherence to evolving professional standards. These trends mirror the European shift toward harmonized reporting advocated by recent cytogenomic guidelines [2] and updated SIGU recommendations (available from the SIGU website).

Oncohematology remained the most challenging diagnostic field. The increase in karyotype reconstruction errors observed in the most recent retrospective evaluation cycles should be interpreted cautiously and may reflect multiple contributing factors, including the complexity of cases derived from routine diagnostic activity and differences in laboratory workflows. At the same time, the reduction in inadequate metaphase number and the disappearance of missing ISCN reports indicate improved technical adequacy and more complete reporting. Overall, these findings suggest that the main residual source of variability lies in the interpretation and formal description of complex clonal architectures. This finding should be interpreted cautiously studies focusing on cytogenetic analysis of hematologic malignancies have shown that even experienced laboratories may struggle with accurate reconstruction and ISCN description of complex or chimeric karyotypes [5, 8, 9]. This finding should be interpreted cautiously and may reflect multiple contributing factors, including the complexity of cases derived from routine diagnostic activity. At the same time, the progressive improvement in ISCN completeness and the reduction in inadequate metaphase counts suggest improved technical adequacy despite persistent interpretive challenges.

Taken together, the Lombardy EQA data indicate consistently high analytical concordance across diagnostic sectors, accompanied by recurrent but progressively reduced variability in interpretation and reporting. This distribution of strengths and weaknesses mirrors national and international EQA experiences in cytogenetics and molecular genetics [1-9] and reinforces the principle that EQA programs are most effective when assessing the entire diagnostic process, not only the technical laboratory component but also reporting structure, clinical interpretation and communication of analytical limitations. Several strategic priorities emerge for future development of the regional program:

- further harmonization of structured reports, including mandatory sections and consistent documentation of key analytical elements;
- ongoing ISCN training, with emphasis on complex oncologic karyotypes and array-derived notations;
- progressive integration of NGS-based methods applied to cytogenomic analysis into the EQA portfolio, reflecting current shifts in diagnostic workflows;
- strengthened collaboration with national and international EQA providers, ensuring dynamic alignment with evolving best-practice standards and improved cross-laboratory comparison.

Within this broader context, the Lombardy cytogenomics EQA program represents a mature and integrated regional implementation of principles developed over two decades of Italian and European efforts in cy-

togenetics quality assurance. Its longitudinal structure, comprehensive inclusion of cytogenomic technologies and strong linkage to regional governance represent important strengths supporting ongoing improvement and harmonization across laboratories.

CONCLUSIONS

The results of the Lombardy cytogenomics EQA program confirm the effectiveness of a regionally coordinated initiative in strengthening the quality and reliability of cytogenomic diagnostics. Between 2018 and 2024, laboratories consistently achieved high analytical concordance across all sectors, accompanied by progressive improvements in reporting completeness, ISCN compliance and adherence to national and international guidelines.

The program proved particularly valuable in identifying persistent critical areas, notably the interpretation and reporting of complex oncologic karyotypes and the standardized communication of methodological limitations. These findings support the implementation of targeted training initiatives and continued harmonization of reporting practices.

Future integration of emerging technologies, including NGS-based cytogenomic approaches, into the EQA framework will be essential to reflect evolving diagnostic workflows. Overall, this experience underscores the value of sustained EQA activities as a public health tool for promoting continuous quality improvement, harmonized laboratory practices and alignment with evolving best practices in cytogenomics.

Authors' contributions

FP: conceived and coordinated the study, supervised data interpretation and drafted the manuscript; GL, GM, BZ, SB: contributed to supervision and manuscript revision; GA, VA, SDM, SR, MI, SS: contributed to data extraction, evaluation and manuscript review. All Authors approved the final manuscript.

Conflict of interest statement

The Authors declare no conflicts of interest.

Use of artificial intelligence

Artificial intelligence tools (ChatGPT, OpenAI) were used exclusively for language editing and stylistic refinement. Scientific content, data analysis and interpretations were entirely performed, reviewed and validated by the Authors.

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