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Guidelines

Molecular Testing in Solid Tumors: Best Practices from the Molecular Pathology and Precision Medicine Study Group of the Italian Society of Pathology (PMMP/SIAPeC)

Shaping Excellence in Molecular Diagnostics

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Summary

The Italian Society of Pathology's Molecular Pathology and Precision Medicine Study Group (PMMP/SIAPeC) has released a three-part set of best practice guidelines to standardize and enhance molecular testing in solid tumors. Part I focuses on the pre-analytical phase, emphasizing proper tissue handling and quality control to preserve nucleic acid integrity. Part II addresses the analytical phase, outlining workflows for next-generation sequencing (NGS), from extraction to variant interpretation, with recommendations on choice of platform, gene panels, and bioinformatics. Part III covers the post-analytical phase, offering guidance on structured, clinically meaningful reporting to support therapeutic decisions, including standards for both tissue and liquid biopsies. Together, these documents aim to harmonize molecular diagnostics, ensuring reliable, high-quality results that support precision oncology.

Key words: Pathology, recommendations, molecular diagnostics, precision medicine, standardization

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In the era of precision oncology, the role of pathologists has expanded beyond traditional morphology to encompass the integration of genomic data into clinical decision-making. Molecular diagnostics – particularly next-generation sequencing (NGS) – are now indispensable tools in the management of solid tumors. However, the clinical utility of these technologies hinges on the quality, consistency, and interpretability of the entire diagnostic process, from tissue collection to final reporting.

In 2022, the Italian Society of Pathology and Diagnostic Cytology (SIAPEC-IAP) – Study Group of Molecular Pathology and Precision Medicine (PMMP) published publicly available recommendations for the annotation, interpretation, and reporting of variants identified through NGS analyses [1]. At that time, most diagnostic applications of NGS relied on small panels targeting a limited set of clinically-actionable genomic alterations at both the DNA (single nucleotide variants, insertions/deletions, copy

number variations) and RNA (gene fusions) levels [2-4]. That document laid the groundwork for standardized reporting practices, supporting the implementation of precision medicine in routine oncologic diagnostics across Italy. Since then, the field has rapidly evolved. The approval of new targeted therapies and companion diagnostics has significantly increased the complexity of NGS-based testing, both in scope and interpretation. In response, the European Society for Medical Oncology (ESMO) released updated guidelines in 2024 addressing the use of NGS in patients with advanced cancer and the clinical reporting of genomic findings [5,6]. The growing number of predictive biomarkers now requires continuous adaptation of diagnostic assays to ensure they capture relevant alterations in routine clinical samples. As a result, comprehensive genomic profiling (CGP) is increasingly being adopted as part of standard practice. In light of these developments, the 2024 SIAPEC-IAP PMMP annual meeting prioritized an update to the 2022 guidelines. An ad hoc working group – comprising molecular biologists, pathologists, and clinical oncologists –was formed under the PMMP mandate to revise and expand the NGS reporting template in alignment with recent scientific and clinical advancements. The present update preserved the foundational structure of the 2022 document while incorporating insights from current literature, practical experience in Italian academic and public laboratories, and input from oncologists [7-10]. New recommendations were also introduced for the use of large gene panels, in line with the 2024 ESMO guidelines [5,6].

To address these needs and promote harmonization across Italian laboratories, the Molecular Pathology and Precision Medicine Study Group of the Italian Society of Pathology (PMMP/SIAPeC) has developed a tripartite document of best practice recommendations, structured around the three cardinal phases of molecular testing: pre-analytical, analytical, and post-analytical. These documents share a common purpose: to ensure that the entire diagnostic pipeline delivers results that are clinically robust, reproducible, and ultimately meaningful for patients and oncologists alike. This effort was coordinated by the "Recommendations for Molecular Reporting Working Group", convened within the SIAPEC-IAP PMMP study group. This multidisciplinary panel included molecular biologists, pathologists, geneticists, and two medical oncologists with recognized experience in cancer molecular profiling. Members were selected based on their pathological, molecular, and clinical expertise and their scientific commitment to advancing NGS reporting. The working group was tasked with developing consensus recommendations and supporting their dissemination through publication. The expert panel met monthly via web conference and collaboratively developed the recommendations. Additional targeted guidance was formulated for three further contexts: CGP using large NGS panels, BRCA testing in combination with homologous recombination deficiency (HRD) signatures, and NGS-based analysis in liquid biopsy settings. The working group reviewed a wide range of diagnostic workflows currently adopted in clinical practice and evaluated them across several parameters, including report length, the presence of a general summary, inclusion of a biomarker results table, formatting efficacy, clinical and therapeutic relevance, clarity of explanation, and test-specific technical details. Focused discussions led to the articulation of key recommendation statements included in the document. The manuscripts were drafted collaboratively and approved by all members of the working group.

The first paper, authored by Caterina Marchiò et al., focuses on the pre-analytical phase, emphasizing the foundational importance of this often-underestimated stage. The accuracy of molecular testing begins not at sequencing, but at specimen collection. This document provides detailed guidance on tissue handling, fixation, and storage, highlighting the importance of adherence to protocols and stringent quality controls to ensure nucleic acid integrity.

The second paper, by Guerini-Rocco et al., explores the analytical phase, covering the core processes involved in the generation and analysis of genomic data. It outlines best practices from nucleic acid extraction through variant interpretation, addressing key topics such as NGS platform selection, gene panel design, bioinformatics workflows, and quality assurance systems – elements essential to both technical reliability and clinical relevance.

The third and final paper, by Buglioni et al., is dedicated to the post-analytical phase, focusing on how data are translated into clinically useful information. A molecular report is not simply a list of variants; it is a clinical document meant to guide therapeutic decisions. This paper provides recommendations on variant annotation, the use of structured and standardized formats, and the clear communication of results, both in tissue and liquid biopsy contexts. Consistent and accessible reporting ensures effective interdisciplinary communication and helps clinicians make well-informed decisions.

Together, these three papers represent a milestone in the standardization of molecular pathology practice in Italy. They reflect a shared commitment to quality, transparency, and the responsible application of precision medicine in routine oncology care. Above all, they serve as a valuable and authoritative resource for the pathology community, supporting professionals

across the country in delivering high-quality, clinically meaningful molecular diagnostics for patients.

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Authors' contribution

All authors contributed equally to the drafting, revision, and final approval of this paper.

Ethical consideration

Not applicable.

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