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Editorial: 2021 European Society for Medical Oncology (ESMO) Recommendations on Laboratory Diagnostics for *RET* Gene Fusions and Mutations: A New Era in Targeted Therapy for *RET*-Altered Solid Tumors

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Abstract During the past four decades, the identification of phenotypic changes in malignant tumor cells has been refined by the standardization of immunohistochemistry methods. Regulatory-approved companion diagnostics were initially developed for immunohistochemistry and to support early tumor tissue-based clinical trials. In the last decade, molecular profiling and gene sequencing data have identified specific molecular targets that have resulted in increasing drug development programs and regulatory approvals. As an example, *RET*-altered cancers include *RET* gene mutations and *RET* gene fusions. In January 2021, the European Society for Medical Oncology (ESMO) published new guidelines for routine clinical laboratory detection of targetable *RET* gene rearrangements and mutations. FDA approval has now been given for selpercatinib for *RET* fusion-positive NSCLC and papillary thyroid cancer, and *RET* mutation-positive thyroid cancer. This Editorial aims to present a brief overview of the evolution of personalized medicine in oncology and how the 2021 ESMO guidelines have anticipated the need to detect targetable *RET*-altered tumors using technology currently available in accredited clinical diagnostic laboratories.

Keywords: **Editorial • Gene Rearrangement • Mutation • Immunohistochemistry • Polymerase Chain Reaction • Sequence Analysis, Protein**

More than 40 years ago, the identification of tumor-associated antigens resulted in diagnostic immunohistochemistry antibody panels in routine diagnostic histopathology. Guidelines for standardization in tissue fixation and processing and the development of specific monoclonal antibodies continued to develop in parallel with automated immunostaining methods and image analysis to quantify the expression of markers for cell proliferation, apoptosis, and cell phenotypes. Prognostic markers were also identified that included hormone receptors and growth factors. All these developments combined to develop personalized and targeted therapy for patients with advanced malignancy.

Personalized medicine in oncology began almost 20 years ago by identifying epidermal growth factor receptor (EGFR) expression using immunohistochemistry [1]. At this time, the first major biomarker clinical trial was conducted that used tumor tissue samples from patients with advanced non-small cell lung cancer (NSCLC) [1]. These first clinical trials identified which patients would respond to the tyrosine kinase inhibitors (TKI), gefitinib [1,2]. Developments in confocal immunofluorescence microscopy allowed for evaluating multiple potential therapeutic targets within one tumor, using an approach termed 'systems pathology' [3]. Also, the realization that an approved companion diagnostic (CDx) was a fundamental requirement to identify and use personalized treatment options for patients with advanced cancer resulted in an increasing number of regulatory-approved targeted therapies [2,4,5].

In the last decade, molecular profiling and gene sequencing data have identified specific molecular targets that have resulted in increasing drug development programs and regulatory approvals. The identification of gene mutations and rearrangements also requires standardization and reliable detection methods.

The *RET* gene, located on the long arm of chromosome 10, encodes a transmembrane glycoprotein receptor that has tyrosine kinase activity [6,7]. *RET* receptor activation triggers several downstream pathways, including RAS-MAPK, PI3K-AKT, and JAK-STAT, which have roles in cell survival and cell proliferation [6,7]. *RET*-altered cancers include *RET* gene mutations and *RET* gene fusions [6,7]

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In January 2021, the European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group published new guidelines for routine clinical laboratory detection of targetable *RET* gene rearrangements and mutations [8]. ESMO has recommended and compared the use of five main laboratory methods for *RET* gene rearrangements and mutations: immunohistochemistry (IHC); fluorescent in-situ hybridization (FISH); reverse transcription-polymerase chain reaction. (RT-PCR); DNA sequencing by next-generation sequencing (DNA-seq NGS); and RNA sequencing by next-generation sequencing (RNA-seq NGS) [8]. ESMO has recommended that FISH and RNA-seq NGS have the highest sensitivity and specificity for detecting targetable *RET* rearrangements and mutations and recommends that DNA-seq NGS is most applicable for use in screening [8].

The timing of the new ESMO guidelines coincides with the recent approvals by the US Food and Drug Administration (FDA) for targeted therapies in *RET*-altered solid tumors [9,10]. Based on safety and efficacy data from phase I/II clinical trials, selpercatinib was recently approved by the FDA for *RET* fusion-positive NSCLC and papillary thyroid cancer, and *RET* mutation-positive thyroid cancer [9,10]. Following the development of the 2021 ESMO guidelines, it is anticipated that more approvals will follow for targeted therapy in *RET*-altered malignancy.

Conclusions

During the past four decades, the identification of phenotypic changes in malignant tumor cells has been refined by the standardization of immunohistochemistry methods. Twenty years ago, the development of regulatory-approved companion diagnostics occurred in parallel with initial clinical trials using human tumor tissue samples, initially from patients with NSCLC. In the past decade, molecular profiling and gene sequencing developments have taken personalized medicine to a new level, as shown by *RET*-altered cancers. The 2021 ESMO guidelines have anticipated the need to detect targetable *RET* gene rearrangements and mutations in patients with advanced malignancy using technology currently available in accredited clinical diagnostic laboratories.

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