THERAPEUTIC ADVANCES in
Medical Oncology

Review

Chinese expert consensus on clinical practice of MET detection in non-small cell lung cancer

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Ther Adv Med Oncol

2024, Vol. 16: 1–19

DOI: 10.1177/17588359231216096

***Abstract*:** Mesenchymal epithelial transition (MET) factor alteration in non-small cell lung cancer (NSCLC) includes MET exon 14 skipping alteration (METex14 skipping), MET gene amplification, MET gene mutation (mainly kinase domain mutation), MET gene fusion, and MET protein overexpression. The incidence of METex14 skipping in patients with NSCLC is 0.9–4.0%. At present, drugs targeting METex14 skipping have been approved in China and other countries like Japan and USA. Patients with advanced NSCLC should undergo testing, including METex14 skipping, to screen the population with benefit from targeted therapy with MET inhibitors. The incidence of *de novo* MET gene amplification in NSCLC patients is 1–5%, the incidence of acquired MET gene amplification in epidermal growth factor receptor tyrosine kinase inhibitor (TKI)-resistant patients is 5–50%, and the incidence in anaplastic lymphoma kinase (ALK) TKI-resistant patients is about 13%; the incidence of MET protein overexpression in NSCLC patients is 13.7–63.7%. Several clinical trials on MET gene amplification and MET protein overexpression are ongoing, which have demonstrated their important guiding significance as biomarkers in the clinical treatment with MET inhibitors. Accurate detection of MET alterations is a prerequisite for MET inhibitor therapy. Since there are many types of MET alterations and related testing methods, as well as many problems and challenges during clinical testing, further sorting and standardization are required. Combined with clinical practice experience, literature review, and expert discussion, the writing group developed this consensus on the three main types of MET alterations (METex14 skipping, MET gene amplification, and MET protein overexpression) in order to guide the practical applications of clinical MET testing.

Keywords: consensus, MET detection, METex14 skipping, MET gene amplification, MET protein overexpression, non-small cell lung cancer

This article is based on a consensus first published in the Chinese Journal of Pathology (Chinese expert consensus on clinical practice of MET detection in non-small cell lung cancer. 2022, 51[11]: 1094-1103; DOI: 10.3760/cma.j.cn112151-20220606-00491). The article is translated and reprinted by permission of Chinese Medical Association.

Received: 19 May 2023; revised manuscript accepted: 6 November 2023.

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Introduction

Lung cancer is one of the most common malignancies in China. According to the latest global cancer data for 2020 published by the WHO International Agency for Research on Cancer (https://gco.iarc.fr/), lung cancer accounted for about 17.9% of new cases of cancer in China, and deaths due to lung cancer accounted for about 23.8%, both of which ranked first in each of these categories. Since the approval of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), in 2003, targeted therapy

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for non-small cell lung cancer (NSCLC) has greatly developed in the past 20 years and significantly prolonged the survival of patients.[1] In addition to the common driver genes EGFR, KRAS, and ALK in NSCLC, other rare driver genes such as ROS1, RET, MET, HER2, and BRAF have also drawn increasing attention.

In 2021, the MET inhibitor savolitinib was approved in China for locally advanced or metastatic NSCLC with MET exon 14 skipping alteration (METex14 skipping). Data from clinical studies of multiple MET inhibitors in advanced NSCLC patients with METex14 skipping have shown favorable efficacy.[2–4] At present, the main guidelines for the diagnosis and treatment of lung cancer, including Guidelines of Chinese Society of Clinical Oncology in NSCLC, Guidelines on Clinical Practice of Molecular Tests in Non-Small Cell Lung Cancer in China (2021 Edition), and the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC, have listed the testing of METex14 skipping as a primary or secondary recommended test item for advanced NSCLC. MET gene amplification is one of the important resistance mechanisms of EGFR-TKI targeted therapy, and the data from multiple clinical trials have shown that advanced NSCLC patients with MET gene amplification can benefit from MET inhibitor therapy, thus it is also recommended to be tested in the above guidelines.[4,5–11] MET protein overexpression has recently shown important potential application value in multiple clinical trials,[8,9–13] attracting more clinical attention over time, and is also recommended for testing in the Chinese Medical Association Guidelines for the Clinical Diagnosis and Treatment of Lung Cancer (2022 Edition). Therefore, this consensus mainly elaborates the clinical significance, target population, test methods and paths, and remaining problems of the above three types of MET alterations, and puts forward relevant suggestions and recommended schemes. In addition, the consensus also standardizes the forms of test reports in order to guide the standardized MET testing in clinical practice, so as to obtain accurate test results, and maximize the benefits for relevant patients.

Method

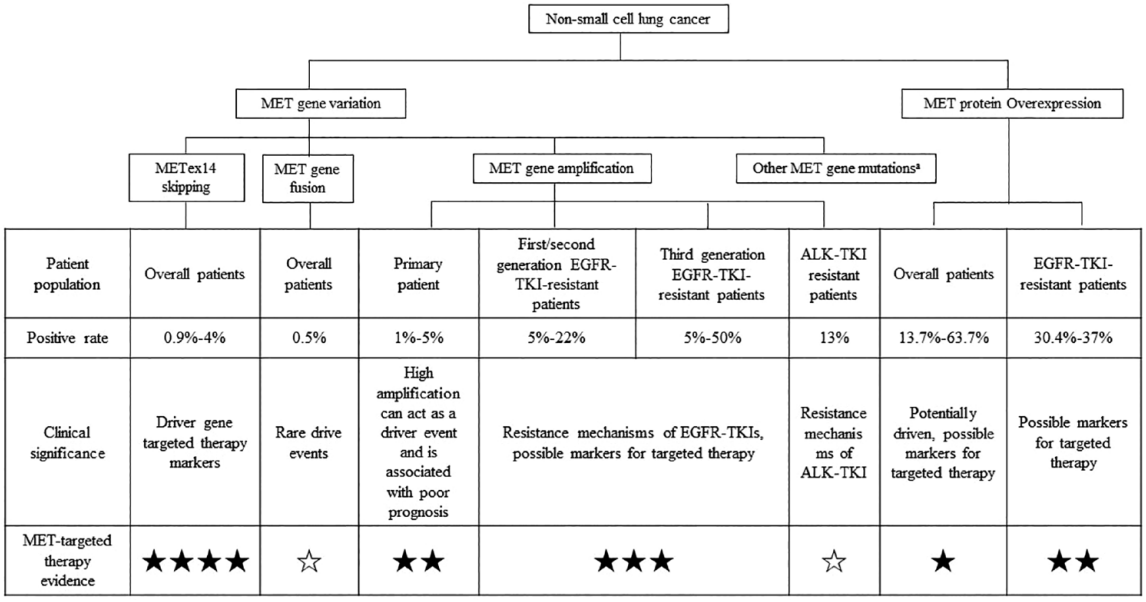
The aim of this consensus-building process was to discuss controversial issues relating to the detection of MET alteration, including METex14 skipping, MET gene amplification, and MET protein expression in NSCLC. This consensus was formed under two rounds of deep discussion by virtual meeting, involving 20 pathologists and 19 clinical experts, listed at the end of the manuscript.

All experts agreed to grade recommendation levels based on levels of evidence. The specific consensus was graded as 'strongly recommended' when: (a) there are sufficient evidence of application request in related to drug approval; b. testing assays were approved, or widely accepted and validated. The specific consensus was graded as 'recommended' when: (a) the application had positive evidence in multiple drug clinical trials and need further evidence without Food and Drug Administration/National Medical Products Administration (FDA/NMPA) approval; (b) testing assays could be an alternative or promising but remained to improve their performance. The final manuscript was reviewed and approved by all panel experts.

MET gene and its clinical significance

The MET gene, also known as c-MET, is a proto-oncogene located on the long arm of human chromosome 7 at position 7q21-31, with a DNA length of approximately 125 kb, which contains 21 exons and 20 introns. The MET protein, encoded by MET, is a tyrosine kinase receptor. Its natural ligand, hepatocyte growth factor (HGF), can bind to the extracellular domain of MET, promote MET dimerization and tyrosine phosphorylation, and activate numerous downstream signaling pathways, such as PI3K-AKT, RAS-MAPK, STAT, and Wnt/β-catenin, thus promoting cell proliferation, cell growth, cell migration, invasion, and angiogenesis, which plays an important role in normal tissue development and tumor progression.[14]

MET alterations, including METex14 skipping, MET gene amplification, MET gene point mutation (mainly kinase region mutation), MET gene fusion, and MET protein overexpression (Figure 1), may lead to abnormal activation of the MET signaling pathway, resulting in tumor development and progression.[15] Among them, METex14 skipping continuously activates downstream signaling by hindering protein degradation; MET gene point mutation, MET gene fusion, and MET gene amplification directly activate MET kinase or lead to increased protein expression,



Patient population	Overall patients	Overall patients	Primary patient	First/second generation EGFR-TKI-resistant patients	Third generation EGFR-TKI-resistant patients	ALK-TKI resistant patients	Overall patients	EGFR-TKI-resistant patients
Positive rate	0.9%-4%	0.5%	1%-5%	5%-22%	5%-50%	13%	13.7%-63.7%	30.4%-37%
Clinical significance	Driver gene targeted therapy markers	Rare drive events	High amplification can act as a driver event and is associated with poor prognosis	Resistance mechanisms of EGFR-TKIs, possible markers for targeted therapy		Resistance mechanisms of ALK-TKI	Potentially driven, possible markers for targeted therapy	Possible markers for targeted therapy
MET-targeted therapy evidence	★★★★	☆	★★	★★★		☆	★	★★

Figure 1. Incidence and clinical significance of MET alterations in non-small cell lung cancer.
[a]Represents limited evidence that MET kinase domain mutations often act as resistance mechanisms to MET inhibitors, the significance of mutations at other sites is unknown.
★★★★: Several registration studies with MET inhibitors have shown that MET inhibitors have definite efficacy and have been approved for the corresponding indications.
★★★: Several registration studies with MET inhibitors are ongoing, and the preliminary benefits of MET inhibitors in this population have been demonstrated in several prospective clinical studies.
★★: The subgroup analyses of several prospective clinical studies have preliminarily yielded the efficacy evidence of MET inhibitor treatment.
★: A single study with small sample size has preliminarily shown the efficacy evidence of MET inhibitor treatment.
☆: Case reports have shown the efficacy evidence of MET inhibitor treatment.

thus continuously activating downstream signaling; overexpression of MET protein level can increase MET receptor on the cell membrane surface, increasing HGF sensitivity, and also leading to abnormal activation of MET pathway.[15] In NSCLC, there are differences in the incidence and clinical significance of different types of MET alterations (Figure 1), of which METex14 skipping, MET gene amplification, and MET protein overexpression are currently of major clinical concern, and this consensus mainly elaborates on these three types of alterations.

1. *METex14 skipping*: MET proteins can be negatively regulated by Casitas B-lineage lymphoma (CBL) E3 ubiquitin ligase-mediated ubiquitination degradation. The juxtamembrane domain encoded by MET exon 14 contains a CBL binding site (Y1003), which is an important region for the negative regulation of MET protein.[16] CBL binds to Y1003 and mediates MET protein ubiquitination, which leads to MET protein degradation.[15] Variants such as deletion of the MET protein juxtamembrane domain, amino acid substitution, or deletion at Y1003 caused by METex14 skipping may lead to impaired MET protein ubiquitination, increased MET stability, and reduced degradation, which causes sustained activation of downstream signaling.[15] The main reported METex14 skipping sites include branch site (mononucleotide), poly-pyrimidine tract (16 nucleotides), splice acceptor site (upstream 2 nucleotides), and splice donor site (downstream 2 nucleotides; Figure 2).[17] Mutations at these sites result in aberrant splicing of the mRNA, as evidenced by MET exon 14 deletion and fusion of exons 13 and 15. METex14 skipping alterations are distributed across a wide range of common sites in various forms, which is a challenge in clinical testing and interpretation (see Appendix Table A1 for commonly reported sites).[18–22] It has been reported that the proportion of NSCLC patients with METex14 skipping ranges from 0.9% to

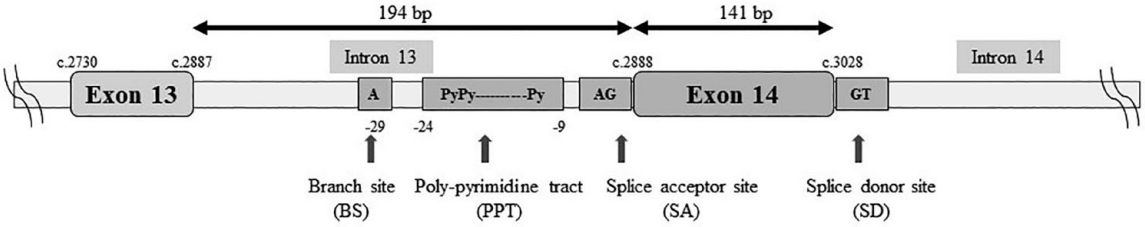


Figure 2. Major distribution sites of MET exon 14 skipping alterations.

2.0% in mainland China,[19,21,23,24] and 2.6%[18] and 3.3%[25] in Hong Kong and Taiwan, respectively, which are slightly lower than that in the foreign population (2% to 4%).[26] METex14 skipping usually occurs in elderly patients,[27] and occurs more frequently in patients with lung adenocarcinoma (approximately 3%)[26] than in patients with lung squamous cell carcinoma (1–2%),[20–28] and is more frequently reported in patients with sarcomatoid carcinoma of the lung (5–32%).[29] Study data showed that 0.3–10.0% of NSCLC patients with METex14 skipping carried EGFR mutations at the same time, and 6.4–28.5% carried EGFR gene amplification.[17] In the absence of MET inhibitors, METex14 skipping is usually associated with high invasiveness, resistance to antitumor therapy, and poor prognosis.[18–30] Data from multiple registered clinical studies have shown that MET inhibitors have demonstrated favorable antitumor activity and safety in advanced NSCLC patients with METex14 skipping (enrolled patients include those with adenocarcinoma, squamous cell carcinoma, and other types of tumors).[2–4] Tepotinib and capmatinib have been successively approved for marketing in Japan and the United States because of their favorable antitumor activity and safety in advanced NSCLC patients with METex14 skipping.[3,4] Savolitinib was approved for marketing by NMPA in June 2021, which is the first highly selective MET inhibitor for the treatment of locally advanced or metastatic NSCLC adult patients with METex14 skipping who have progression after platinum-based chemotherapy or cannot tolerate standard platinum-based chemotherapy in China. Relevant clinical trials of other MET small molecule inhibitors (such as glumetinib and bozitinib) in NSCLC patients with METex14 skipping are still ongoing.

[Consensus 1] METex14 skipping is one of the driver gene mutations in advanced NSCLC and is an important molecular marker for screening the benefit population of targeted therapy with MET inhibitors.

2. *MET gene amplification*: MET gene amplification refers to an increase in the gene copy number (GCN), including focal amplification and polysomy. Focal amplification refers to an increase in GCN of MET (or merged surrounding regions), with no significant increase in GCN in other regions of the chromosome. Polysomy refers to an increase in the copy number of the entire chromosome (or larger segments of the chromosome). Both forms may lead to upregulation of MET mRNA levels, further increasing MET protein expression, and thereby increasing MET pathway signaling in the activated state.[30] MET gene amplification can be used as one of the driver gene variants in primary tumors and has been found in a variety of solid tumors, with primary MET gene amplification occurring in 1–5% of NSCLC.[30] MET gene amplification is associated with a higher histologic grade, an advanced clinical stage, and a poor outcome. Limited clinical data (Study PROFILE 1001,[5] Study GEOMETRY mono1,[4] Study VISION[6]) suggest that MET inhibitors may benefit advanced NSCLC patients with primary MET gene amplification (there are some differences in primary MET gene amplification cut-offs between studies). MET gene amplification is more frequently occurred after targeted therapy in NSCLC patients with other positive driver genes and is one of the

important mechanisms of EGFR-TKI resistance. Acquired MET gene amplification, as a bypass signaling pathway, leads to resistance by bypassing EGFR activation downstream pathways when EGFR signaling is inhibited by EGFR-TKIs. After resistance to different generations of EGFR-TKIs, the proportion of MET gene amplification varies. According to the data presented in the literature, the proportion of MET gene amplification after resistance to the first- and second-generation EGFR-TKIs ranges from 5% to 22%,[31,32] the proportion of MET gene amplification after resistance to the third-generation EGFR-TKI osimertinib as a first-line treatment ranges from 7% to 15%, and 5% to 50% after resistance to osimertinib as a second-line treatment.[33] In addition to EGFR-TKIs, MET gene amplification is also one of the resistance mechanisms for ALK-TKIs, and the proportion of MET gene amplification after resistance to the second- and third-generation ALK-TKI treatments is about 13%.[34] Data from clinical studies suggest that EGFR-TKIs combined with MET inhibitors may be a potential treatment strategy for EGFR-TKI-resistant patients due to secondary MET gene amplification.[7–11] Data from the TATTON study showed that patients with MET focal amplification and polysomy after EGFR-TKI resistance showed some clinical efficacy with osimertinib combined with savolitinib treatment, with an objective response rate of 30% in the overall population with MET gene amplification ($n = 53$) and 31% and 28% in the population with focal amplification ($n = 35$) and population with polysomy ($n = 18$), respectively.[35] The results of the SAVANNAH study showed that osimertinib combined with savolitinib showed good clinical efficacy in patients with high MET amplification (Fluorescence in situ hybridization, FISH GCN $\geqslant 10$) after osimertinib resistance.[9] Another report showed that MET inhibitor treatment in patients who developed MET gene amplification after ALK-TKI resistance also achieved some degree of efficacy[34]; thus, this treatment scheme is worthy of further exploration and investigation.

[Consensus 2] MET gene amplification is a primary driver gene mutation in NSCLC and one of the important resistance mechanisms to EGFR-TKIs and ALK-TKIs, which can be used as a potential molecular marker for combined targeted therapy after drug resistance in advanced patients; therefore, MET gene amplification testing should be emphasized in clinical practice.

3. *MET protein overexpression*: Studies have shown that the proportion of patients with MET protein overexpression who suffer from NSCLC ranges from 13.7% to 63.7%,[36–38] and the incidence of MET protein overexpression in EGFR-TKI-treated advanced NSCLC patients with EGFR mutations ranges from 30.4% to 37.0%.[12,38] Recent data have shown that Teliso-v, a MET antibody conjugate, has demonstrated a clinically meaningful tumor response in advanced treated NSCLC patients with wild-type EGFR and MET protein overexpression [$\geqslant$ 50% tumor cells strong positive by immunohistochemistry (IHC) (3+)].[12] Based on this phase II study, FDA approved the Teliso-v Breakthrough Therapy Designation and the corresponding phase III clinical study (NCT04928846) is ongoing, suggesting that MET protein overexpression can act as a biomarker for targeted therapy in patients with advanced NSCLC. A phase III clinical study (SANOVO, CTR20211427) in treatment-naïve advanced NSCLC patients with EGFR mutation combined with MET protein overexpression is also ongoing. Studies, such as INSIGHT and TATTON, have shown that patients with MET IHC $\geqslant$ 50% of tumor cells 3+ after EGFR-TKI resistance may benefit from EGFR-TKI combined with MET inhibitor therapy, whereas the subgroup with IHC $\geqslant$ 50% of tumor cells moderately positive (2+) does not respond well to combined targeted therapy.[7,9–13] The SAVANNAH study showed that patients with MET IHC $\geqslant$ 90% of tumor cells 3+ after osimertinib resistance could benefit from osimertinib when combined with savolitinib,[9] further identifying the important value of MET protein overexpression as a biomarker.

Another study has explored the correlation between MET protein overexpression and METex14 skipping or MET gene amplification, and the result showed that MET protein expression levels were less correlated with METex14 skipping.[39–41] The NCCN guidelines for NSCLC (3rd edition, 2022)

also clearly state that IHC is not recommended as a screening method for METex14 skipping. In the TATTON study, MET gene amplification (MET GCN ⩾5 or MET/CEP7 ⩾2) was also detected in 80% of patients who developed MET protein overexpression (⩾ 50% tumor cells 3+) after EGFR-TKI resistance.[35] Another study in 181 patients with lung adenocarcinoma without targeted therapy showed MET gene amplification in only 1% of patients with MET protein overexpression (IHC H-score ⩾200).[40] Thus, MET protein overexpression may be caused by multiple reasons, and the association with MET gene amplification needs to be further explored in more studies. At present, data on detection antibodies and positive cut-offs are sparse, and further clinical studies are needed to accumulate clinical experience.

[Consensus 3] MET protein overexpression has potential guidance value in the clinical treatment of MET inhibitors in NSCLC, although the cut-off of benefit in different patient populations still requires further study.

Target populations for MET testing

[Consensus 4] METex14 skipping testing is strongly recommended for advanced NSCLC patients; MET gene amplification testing is recommended for advanced NSCLC patients who are treatment-naive and EGFR-TKI-resistant.

Types and treatment of common samples for testing

The types of samples used for MET testing mainly include tumor tissue samples, cytological samples, and liquid samples. METex14 skipping can be detected by RNA, and relevant samples should be fixed in time, and stored appropriately, to prevent RNA degradation.

1. *Tumor tissue samples*: Paraffin-embedded tumor tissue samples, including surgical and biopsy samples, are preferentially used. Before testing, the proportion of tumor cells needs to be assessed to ensure that the testing requirements are met. For surgical samples, samples with a higher proportion of tumor cells are preferentially selected for testing.
2. *Cytological samples*: including pleural and peritoneal effusion, bronchial brushing, endobronchial ultrasound-guided fine-needle aspiration biopsy samples, sputum, bronchoalveolar lavage fluid, etc. The testing should be performed after cell evaluation, or the samples should be made into paraffin-embedded samples, and the testing should only be performed after evaluation for the testing requirement.
3. *Liquid biopsy samples*: For patients with advanced NSCLC who cannot provide tissue or cytological samples, blood tests may be considered for METex14 skipping. Circulating tumor DNA (ctDNA) is present in the plasma of patients and can be genetically tested. The cerebrospinal fluid of some advanced NSCLC patients with meningeal metastasis has an enriched effect for ctDNA in the intracranial tumors, thus relevant testing can also be considered. Compared with tissue samples, the ctDNA content in blood and cerebrospinal fluid is very low, implying a poor sensitivity compared with tissue sample testing.

Commonly used MET testing methods

As for MET alterations in NSCLC, common molecular testing methods mainly include IHC, FISH, reverse transcription quantitative real-time Polymerase Chain Reaction (RT-qPCR), Sanger sequencing, and next-generation sequencing (NGS) technology. Different molecular testing methods have their own advantages and disadvantages and are also affected by MET variant types, sample types, sample quality, tumor content, and laboratory conditions.

Testing method for METex14 skipping

The testing methods for METex14 skipping include Sanger sequencing, RT-qPCR, and NGS based on DNA or RNA levels, among which Sanger sequencing is seldom used in current clinical practice because of its low detection throughput and sensitivity. Thus, this consensus does not require further introduction. At present, the commonly used methods in clinical practice are shown in Table 1.

1. *RT-qPCR*: Using RNA as the testing object, primers are designed in the exon 13 and 15 regions of MET to detect whether there are specific amplification products. This method is highly accurate when detecting METex14 skipping,[22] but it may miss detection for some special and rare forms of MET variants functioning similar to

Table 1. Common testing methods for MET exon 14 skipping alteration in non-small cell lung cancer.

Methods	Principles	Applicable sample types	Advantages	Disadvantages	Recommendation level
RT-qPCR	MET exon 13/15 fusion testing by fluorescent PCR following reverse transcription at the mRNA level	Tissue and cytological samples	High accuracy, high platform accessibility, and short cycle	RNA is easily degraded, so it requires samples with high quality	Strongly recommended
DNA-based NGS	DNA is used as the testing object, amplicon method or hybrid-capture method is used to construct the library and enrich METex14 skipping-related region fragments for gene sequence testing	Tissue and cytological samples	High throughput and high accuracy	Detection rates are influenced by primer design or probe coverage and bioinformatics analysis capabilities, with relatively long testing cycles	Strongly recommended
		Liquid biopsy samples	High throughput and high sample accessibility	High false negative rate	Recommended
RNA-based NGS	RNA is used to test MET exon 13/15 fusion by reverse transcription and library construction	Tissue and cytological samples	High throughput and high accuracy	High sample quality, relatively long test cycle and relatively low accessibility	Strongly recommended

NGS, next-generation sequencing; RT-qPCR, reverse transcription quantitative real-time PCR.

METex14 skipping, such as amino acid substitution (approximately 2% of overall positives[20]) or deletions at Y1003.[30] For patients whose test results are near the positive cut-off, these results should be interpreted cautiously and the analysis of which should be combined with sample quality, tumor cell content, and test quality control. Additional platforms may be used for retesting if necessary.

2. *DNA-based NGS*: Tumor tissue samples or cytological samples are preferred for testing. At present, the kit is mainly based on two library construction methods, amplicon method and hybrid-capture method, through which METex14 skipping-related region fragments are enriched for gene sequence testing. Considering the variation sites and form diversity of METex14 skipping, the test ability of different library construction methods also varies, and it is recommended that the targeted sequences for library construction should cover at least 50 bp of all MET 13 introns, MET 14 exons, and MET 14 exons downstream (within MET 14 introns). Database for NGS bioinformatics analysis should contain comprehensive METex14 skipping site information as much as possible and be updated regularly. For suspected METex14 skipping detected, it is recommended to be supplemented with RT-qPCR or RNA sequencing validation on the basis of bioinformatics analysis prediction. The DNA-based NGS platform can also achieve high sensitivity and specificity after adequate optimization based on the above factors. When tumor tissue samples and cytological samples are not available, liquid biopsy samples may be considered for DNA-based NGS. ctDNA has a low content in cancer patients and its detection requires a testing method with high sensitivity, thus it is possible to have false negative results; ctDNA testing will also be affected by the coverage of the detection probe. Therefore, these limitations need to be fully considered when testing liquid samples, and the possibility of false negatives should be noted when negative results occur.
3. *RNA-based NGS*: It is performed to detect MET exon 13/15 fusions at the RNA level to determine whether METex14 skipping occurs. This method directly tests METex14 skipping, with clear testing coverage and simple bioinformatics analysis.

Table 2. Common testing methods for MET gene amplification in non-small cell lung cancer.

Methods	Principles	Applicable sample types	Advantages	Disadvantages	Interpretation criteria recommended	Recommendation level
Fluorescence *in situ* hybridization	Fluorescent probes are used to label *in situ* MET gene and chromosome 7 centromere (CEP), and MET copy number (GCN) and MET/CEP7 ratio in tumor cells are directly observed and calculated in combination with morphology	Tissue and cytological samples	Direct calculation of MET and chromosome 7 signals in tumor cells, which is the gold standard for gene amplification testing and can distinguish polysomy from local amplification; and fewer samples required	Single gene testing; lack of uniform judgment criteria	Recommended positive cut-off is MET GCN ⩾ 5 or MET/CEP7 ⩾ 2	Strongly recommended
DNA-based NGS	Copy number changes are calculated based on comparison of sequencing signal and percent cell tumor between the tested and control samples	Tissue and cytological samples	High throughput	Low maturity due to tumor cell percentage and bioinformatics algorithm, and it needs to be verified	No uniform interpretation criteria; FISH retest is required if necessary	Acceptable
		Liquid biopsy samples	High throughput and high sample accessibility	Low sensitivity	Same as above	Acceptable

CEP7, chromosome 7 centromere; GCN, gene copy number; NGS, next-generation sequencing.

Especially when patients develop atypical intronic mutations affecting splicing, this method can promote the identification of METex14 skipping. However, as with RT-qPCR, missed detection may occur for some rare forms of MET variants (e.g. amino acid substitution or deletion at Y1003). RNA-based NGS also requires high sample quality, and quality control should be done well throughout the testing process.

[Consensus 5] METex14 skipping can be detected by RT-qPCR, DNA-based NGS, or RNA-based NGS. Different testing methods have their own advantages and disadvantages and can verify or supplement each other when necessary. METex14 skipping sites are diverse; thus, it requires special attention in clinical testing and interpretation.

MET gene amplification testing method

At present, the testing methods for MET gene amplification mainly include FISH and NGS. Currently, the judgment criteria and clinical benefit cut-off of MET gene amplification have not been clarified; therefore, this consensus is recommended only based on published literature data and commonly used testing methods and reference criteria in clinical studies (Table 2). Further clarification is required based on clinical study data in the future.

1. *FISH*: With FISH, the MET gene is labeled *in situ* with fluorescent probes, and then the number of MET fluorescence signals in tumor cells can be directly observed, so as to calculate the MET gene GCN in tumor cells in combination with their morphology; or the MET/CEP7 ratio in tumor cells can be calculated by labeling the MET gene and chromosome 7 centromere (CEP7). Amplification can be clinically judged by the MET GCN as well as the MET/CEP7 ratio, which can distinguish local amplification from polysomy, and this testing method is currently the gold standard for testing MET gene amplification. There is no uniform interpretation criteria for MET gene amplification by FISH, so the UCCC (University of Colorado Cancer Center)

criteria and the Cappuzzo criteria are primarily referred to. In clinical trials related to MET gene amplification following EGFR-TKI resistance, MET GCN $\geqslant 5$ or MET/CEP7 $\geqslant 2$ are chiefly used as enrollment criteria.[7,10] This consensus recommends this enrollment criterion to serve as an interpretive reference cut-off. Local amplification can be determined when MET/CEP7 $\geqslant 2$; polysomy can be judged when MET GCN $\geqslant 5$ and MET/CEP7 < 2. The MET gene amplification cut-off with predictive value for efficacy may be adjusted based on the results obtained from future clinical studies.

2. *DNA-based NGS*: The DNA-based NGS method can calculate the copy number variation of the MET gene based on sequencing depth, specific site variation frequency, and other information, and tumor tissue samples or cytological samples are preferred in this method. The NGS panel and bioinformatics analysis strategy used by different companies or laboratories may vary, and the presentation form of the test results may also vary. At present, FISH is mostly used to enroll patients with MET gene amplification in clinical studies. It has been reported that the positive concordance rate between NGS (proportion of tumor cells $\geqslant$10%, sequencing depth $\geqslant$500×) and FISH for MET gene amplification in the tissue is about 62.5%.[42] In the TATTON study, the positive concordance rate between NGS (proportion of tumor cells $\geqslant$20%, sequencing depth $\geqslant$200×) and FISH for MET gene amplification in the tissue is 48%.[43] Further analysis has revealed that the positive concordance rate between NGS and FISH for MET local amplification is 88%, and the positive concordance rate between NGS and FISH for MET polysomy is only 4%. The testing of MET gene amplification by NGS requires further optimization and validation. Therefore, it is recommended that the NGS products approved by the NMPA or fully validated be used in clinical practice to test the MET gene amplification. Blood samples are also an important source of testing samples when testing following EGFR-TKI resistance due to the challenges in obtaining tissue samples from needle biopsies. In the TATTON study, ctDNA NGS resulted in a 25% positive concordance rate for MET gene amplification (43% for local amplification and 10% for polysomy) compared with tissue FISH.[43] Therefore, there are still challenges in testing MET gene amplification by NGS with blood samples at this stage, which require further optimization and validation. Tissue samples should be preferentially used for testing, but if no tissue samples are available, blood testing can be done. But a negative test result does not mean that the MET gene amplification can be completely excluded, and a second biopsy FISH retest should be considered if necessary.
3. *Exploration of new methods for testing MET gene amplification*: Droplet digital PCR (ddPCR) is used to analyze the fluorescence signal of each droplet after amplification reaction of the droplet system. The results will be modeled as a Poisson distribution, and the copy number and concentration of target molecules will be obtained by reading the number and proportion of positive droplets of target and internal reference nucleic acids. This method has been explored in the field of MET gene amplification testing, especially blood testing[44–45]; however, it still needs further optimization and validation before any clinical application.

[Consensus 6] MET gene amplification can be tested by FISH and NGS. FISH is the gold standard for the testing of MET gene amplification. The testing of MET gene amplification by NGS still needs further optimization and validation.

MET protein overexpression testing method

MET protein overexpression is tested by IHC. Based on the principle of specific binding of antigens to antibodies, chromogenic agents (fluorescein, enzymes, metal ions, isotopes, etc.) of labeled antibodies are developed through chemical reactions to determine the antigens (peptides and proteins) in tissue cells to perform antigen localization, characterization, and relative quantification. At present, many antibodies for testing MET have been filed for domestic medical devices, involving multiple clone numbers. There are differences in the staining performance of different antibodies, and there is no unified interpretation standard.

Current interpretation standards for clinical studies integrate the intensity and the percentage of

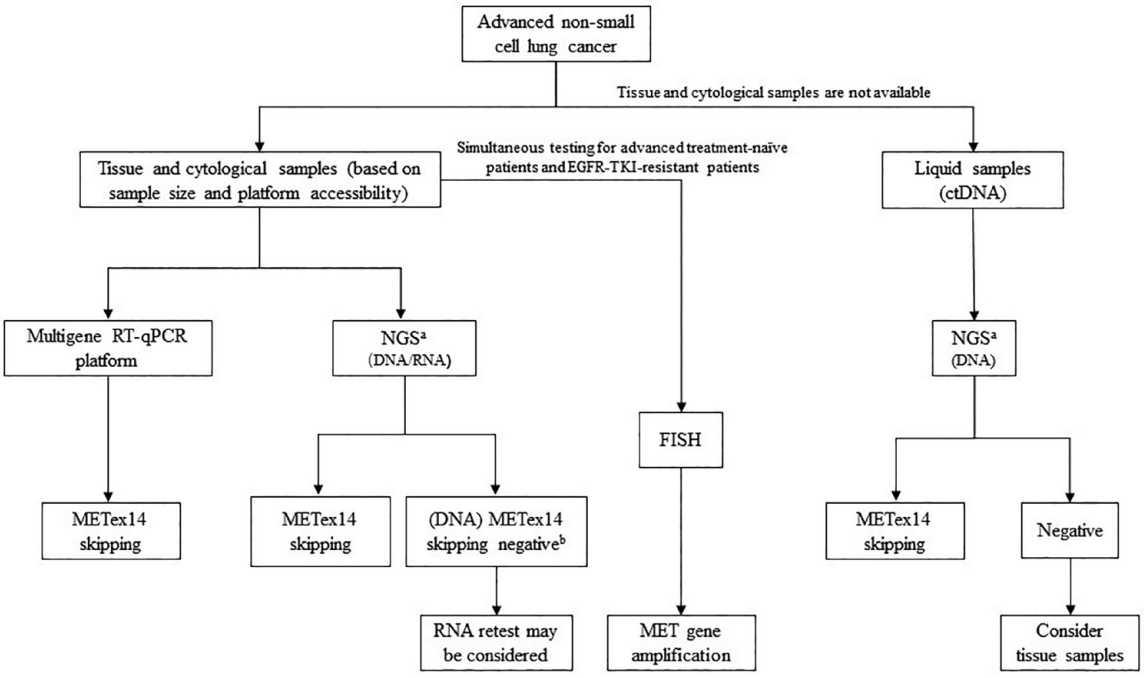


Figure 3. MET testing path in non-small cell lung cancer.
[a]NGS has been used in the clinical practices to test MET gene amplification, but it requires further optimization and validation.
[b]When the results for other driver genes are also negative.
NGS, next-generation sequencing.

expression of relevant antibodies in tumor cells. In TATTON and SAVANNAH studies, patients with MET IHC ⩾ 50% strong tumor cell staining (3+) (using antibody clone SP44) were enrolled[7]; in INSIGHT study, patients with ⩾50% strong (3+) or moderate (2 +) tumor cell staining (using antibody clone D1C1) were enrolled[10]; and in NCT01610336 study, patients with ⩾ 50% strong (3 +) or moderate (2 +) tumor cell staining (using antibody clone 3077) were enrolled.[11] In view of the current diversity of antibodies and the fact that the interpretation standards have not yet been unified, it is necessary to conduct comparative studies on the consistency of different antibodies, and more clinical studies are needed to confirm the clinical value of MET protein overexpression and further clarify the interpretation standard and benefit cut-offs. At current stage of clinical studies, it is recommended that IHC test results should include at least the information of the antibodies used, the percentage of positivity in tumor cells, and the staining intensity.

MET testing path

The pathologist should reasonably select the testing methods and consider multi-platform mutual verification, when necessary, according to the abnormal MET pattern being detected by incorporating a comprehensive evaluation of the type of samples for testing, the number and type of genes tested, testing cost, testing laboratory capacity conditions, and reagent certification. This consensus is based on current evidence and clinical practice, and the MET testing pathway recommended by the expert panel for NSCLC is shown in Figure 3. The testing pathway may be updated in the future based on relevant evidence.

For patients whose tumor tissue/cytological samples are available, according to the accessibility of the laboratory platform, it is preferred to use multi-gene combined testing, including EGFR, KRAS, ALK, ROS1, RET, and MET genes,[46] which can maximize the use of samples to obtain more comprehensive genetic information. When tissue/cytological samples are sufficient, a NGS or multi-gene RT-qPCR platform is recommended; when tissue/cytological samples are insufficient, relevant single-gene testing can be preferred according to clinical needs and clinicopathological characteristics. When the DNA-based NGS platform test results show the

completely negative for driver gene or suspected positive for METex14 skipping, RT-qPCR or NGS based on RNA level can be considered to retest METex14 skipping and other fusion genes. When tissue samples/cytological samples are unavailable, liquid samples can be considered for NGS to test METex14 skipping. In the case of negative results, the possibility of a false negative should be indicated. It is recommended to retest tumor tissue samples if necessary.

FISH is recommended to test MET gene amplification in patients with advanced NSCLC, especially in EGFR-TKI-resistant patients. MET gene amplification has been tested by NGS in clinical practice, but further optimization and validation are still required. In addition, given the potential value of MET protein overexpression in guiding the clinical treatment with MET inhibitors in NSCLC, IHC may be considered to test MET protein overexpression when sufficient tumor tissue is available.

[Consensus 7] Tumor tissue/cytological samples are preferred for MET testing in advanced NSCLC. Multi-gene combined testing platforms, including MET (RT-qPCR or NGS), are used to test METex14 skipping. RNA samples may be considered for supplementary testing when the DNA-based NGS results are negative. FISH is recommended for MET gene amplification in advanced NSCLC patients, especially in EGFR-TKI-resistant patients. When tissue/cytology samples are not available, liquid biopsy samples may be chosen for METex14 skipping testing (Table 3).

MET Test Report specifications and other precautions

Reporting specifications

The test report should include the patient's basic information, pathological information of samples, test methods, test reagents and detection system, quality control information, test results, interpretation of variations, clinical notes, necessary comments, and other key information. In the comments section of the report, it is recommended to include information on the limitations of the test method, special circumstances in the test, and further work. This consensus' recommended report specifications are for MET testing only.

1. *METex14 skipping report specification*: The DNA-based NGS report should include a clear variant name description (METex14 skipping), mutation site information, variant allele frequency, and reference transcript information (NM_000245 and NM_001127500 are commonly used transcripts for MET gene testing, and special attention should be paid to the difference between their sequence number). The report should clearly indicate whether the variation causes METex14 skipping, and for those whose testing results cannot be clearly identified as METex14 skipping, it should be explained in the interpretation of the variation. It is recommended that MET exon and intron coverage should be reflected in the test method section so that the physician can fully assess the testing capability. The mutation name 'METex14 skipping' should be identified in RNA testing (RT-qPCR and RNA-based NGS) reports.
2. *MET gene amplification report specifications*: It is recommended that the FISH test report should include at least the number of tumor cells assessed, mean MET copies/cell, mean CEP7 copies/cell, the ratio of mean MET copies to mean CEP7 copies, and the proportion of tumor cells undergoing amplification. MET gene amplification status should be determined according to the judgment criteria, and local amplification and polysomy should be distinguished when the result is positive. The NGS test report shall include a clear variant information description, GCN information, and the cut-off value for positive determination of MET GCN variation by the test platform. For the NGS report using liquid samples for MET gene amplification testing, in addition to the above information, considering that the sensitivity of liquid testing is currently low, the report should indicate the information related to the high false negative rate.

Other precautions

1. *Inter-laboratory quality control and inter-laboratory quality assessment should be performed.* Laboratories performing MET testing should establish and optimize standardized testing procedures for performance verification prior to clinical testing. Positive and negative controls should be set up in

Table 3. Key points in Chinese expert consensus on clinical practice of MET detection in NSCLC.

Item	Key points in expert consensus recommendations	Recommendation level
MET gene and its clinical significance		
[Consensus 1]	METex14 skipping is one of the driver gene mutations in NSCLC and is an important molecular marker for screening the benefit population of targeted therapy with MET inhibitors	Strongly recommended
[Consensus 2]	MET gene amplification is a primary driver gene mutation in NSCLC and one of the important resistance mechanisms to EGFR-TKIs and ALK-TKIs, which can be used as a potential molecular marker for combined targeted therapy after drug resistance in advanced patients; therefore, MET gene amplification testing should be emphasized in clinical practice	Recommended
[Consensus 3]	MET protein overexpression has potential guiding value in the clinical treatment of MET inhibitors in NSCLC, and the cut-off of benefit in different patient populations still requires further study	Recommended
Target populations for MET testing		
[Consensus 4]	METex14 skipping testing is strongly recommended for advanced NSCLC patients; MET gene amplification testing is recommended for advanced NSCLC patients who are treatment-naïve and EGFR-TKI-resistant	Strongly recommended
Commonly used MET testing methods		
[Consensus 5]	METex14 skipping can be detected by RT-qPCR, DNA-based NGS, or RNA-based NGS. Different testing methods have their own advantages and disadvantages and can verify or supplement each other when necessary. METex14 skipping sites are diverse, thus it requires special attention in clinical testing and interpretation	Strongly recommended
[Consensus 6]	MET gene amplification can be tested by FISH and NGS. FISH is the gold standard for the testing of MET gene amplification. The testing of MET gene amplification by NGS still needs further optimization and validation	Recommended
MET testing path		
[Consensus 7]	Tumor tissue/cytological samples are preferred for MET testing in advanced NSCLC. Multi-gene combined testing platforms including MET (RT-qPCR or NGS) are used to test METex14 skipping. RNA samples may be considered for supplementary testing when the DNA-based NGS results are negative. FISH is recommended for MET gene amplification in advanced NSCLC patients, especially in EGFR-TKI-resistant patients. When tissue/cytology samples are not available, liquid biopsy samples can be chosen for METex14 skipping testing	Strongly recommended

ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

testing. All operations should be performed by trained personnel. Designated personnel shall be responsible for quality monitoring and organizing regular training and comparative analysis of data. At the same time, the testing laboratory should regularly participate in inter-laboratory quality control to ensure the accuracy of the testing

operation and the effectiveness of the test results.

2. *Effective communication should be strengthened for clinical pathology.* MET alterations are more complex than other genetic variants: METex14 skipping has complex and diverse variant loci and forms; MET gene amplification and overexpression criteria have not been unified, and the cut-off is not clear. All of these challenge clinical interpretations of MET test results. It is recommended to establish a clinicopathological communication mechanism to ensure timely communication of information about clinical pathology.

Declarations

Disclaimer

This is a secondary publication (complete translation) of a primary publication titled '[Chinese expert consensus on clinical practice of MET detection in non-small cell lung cancer]' originally published in Chinese in the Chinese Journal of Pathology. Full citation details of the original publication can be found on the first page of the current article, underneath the abstract.

The content of the expert consensus on clinical practice published in this article is jointly discussed and developed by the members of the expert panel based on available medical evidence and practical experience to help relevant personnel perform MET testing or clinical decision-making for non-small cell lung cancer. Its content may not be comprehensive or adequate. Medical knowledge has been rapidly developing, and new evidence may emerge from the time this consensus is generated until publication, which may not be reflected in this consensus. In addition, due to the influence of different factors on the test decisions or results, such as many test methods, complex test procedures, differences in laboratory conditions, and individual differences between patients, the contents of this consensus should be adopted in combination with the test conditions, policy licenses, and independent professional judgment of professionals. The use of this consensus content is voluntary. The members of the expert panel explicitly deny any commercial interest in any of the products mentioned herein. The expert panel shall not be liable for any personal injury or property damage, or any error or omission, caused by or associated with the use of the contents of the consensus.

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Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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Acknowledgements
The authors would like to acknowledge Diagnosis team and medical team from AstraZeneca Pharmaceuticals (China), for the assistance of data collection and manuscript preparation.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Innovation Group Project of Shanghai Municipal Health Commission (2019CXJQ03); Shanghai Municipal Key Clinical Specialty (shslczdzk01301).

Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All information in this consensus can be found in the references.

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Appendix

Table A1. Reported mutation sites of MET exon 14 skipping alterations.

c.2887+11_3029-1118del	c.2888-28_2888-3del	c.2888-17_2888-1delinsAA	c.3012_3028+7del
c.2887+40_3028+441del	c.2888-28_2888-3delinsAAAC	c.2888-17_2953del	c.3015_3028+3del
c.2887+50_3028+49del	c.2888-28_2888-2del	c.2888-16_2888-4del	c.3017_3028+3del
c.2887+91_3028+3del	c.2888-28_2888-1del	c.2888-16_2888-4delinsC	c.3017_3028+4del
c.2887+95_3028+53del	c.2888-28_2896del	c.2888-16_2888-3del	c.3018_3028+1 del
c.2888-160_2900del	c.2888-27_2888-16del	c.2888-16_2888-1delinsAAC	c.3018_3028+2del
c.2888-146_2945del	c.2888-27_2888-14del	c.2888-16_2889del	c.3018_3028+5del
c.2888-132_2930delinsCCCTAA	c.2888-27_2888-10del	c.2888-16_2890del	c.3018_3028+8del
c.2888-104_3028+266del	c.2888-27_2888-10delinsT	c.2888-16_2918del	c.3019_3028del
c.2888-90_2899del	c.2888-27_2888-6del	c.2888-15_2888-4del	c.3019_3028+3del
c.2888-90_2933del	c.2888-27_2890del	c.2888-15_2888del	c.3019_3028+5del
c.2888-82_3028+399del	c.2888-26_2888-10del	c.2888-15_2893del	c.3020_3028+2del
c.2888-71_3029-1180del	c.2888-26_2888-5del	c.2888-15_2899del	c.3020_3028+22del
c.2888-69_2889del	c.2888-26_2892delinsCGCT	c.2888-15_2900del	c.3020_3028+24del
c.2888-69_3028+530del	c.2888-25_2893del	c.2888-15_2913del	c.3021_3028+4del
c.2888-62_2888-14del	c.2888-24_2888-15del	c.2888-15_2915delinsT	c.3021_3028+9del
c.2888-59_3028+1del	c.2888-24_2888-13del	c.2888-14_2888-4del	c.3021_3028+9delinsGGTATATTTT
c.2888-56_2888-28delinsGG	c.2888-24_2888-6del	c.2888-14_2888-3del	c.3021_3036del
c.2888-55_2928delinsA	c.2888-24_2888-1del	c.2888-14_2888-2del	c.3022_3028+1del
c.2888-52_2927delinsCC	c.2888-24_2897del	c.2888-14_2890del	c.3022_3028+4del
c.2888-48_2888-29del	c.2888-23_2888-10del	c.2888-14_2895del	c.3022_3028+5delinsG
c.2888-47_2888-26delinsGGT	c.2888-23_2889del	c.2888-14_2900delC	c.3022_3028+13del
c.2888-46_2888-15del	c.2888-23_2891del	c.2888-14_2905del	c.3022_3028+14del
c.2888-45_2888-18del	c.2888-23_2895del	c.2888-13_2888-2del	c.3023_3028+8 del
c.2888-44_2891del	c.2888-23_2918del	c.2888-13_2888del	c.3023_3028+9del
c.2888-43_2888-18del	c.2888-22_2888-12del	c.2888-13_2908del	c.3023_3028+13del
c.2888-42_2888-2del	c.2888-22_2888-8del	c.2888-12_2888-3del	c.3023_3028+13delinsATA
c.2888-41_2888-21del	c.2888-22_2888-4del	c.2888-11_c.2904del	c.3023_3028+17del
c.2888-40_2888-23del	c.2888-22_2888-3del	c.2888-10_2891del	c.3023_3028+20del
c.2888-40_2888-19del	c.2888-22_2888-2del	c.2888-9_2888-7delinsGG	c.3024_3028del

(Continued)

Table A1. (Continued)

c.2888-39_2890del	c.2888-22_2911del	c.2888-9_2908del	c.3024_3028+7del
c.2888-37_2888-20del	c.2888-21_2888-13delinsAAGCT	c.2888-9_2951del	c.3024_3028+12del
c.2888-37_2888-18del	c.2888-21_2888-9del	c.2888-8_2913del	c.3024_3028+13del
c.2888-36_2888-29del	c.2888-21_2888-7del	c.2888-8_2924delinsTAAA	c.3024_3028+14del
c.2888-36_2888-26delinsAGACG	c.2888-21_2888-6del	c.2888-7_2920del	c.3024_3028+20del
c.2888-36_2888-21del	c.2888-21_2888-5del	c.2888-6_2888-2delinsG	c.3025_3028+1del
c.2888-36_2888-20del	c.2888-21_2888-2del	c.2888-6_2920del	c.3025_3028+2del
c.2888-36_2888-12del	c.2888-21_2888delinsG	c.2888-5_2890delinsATA	c.3025_3028+3del
c.2888-36_2888-2del	c.2888-21_2889delinsAA	c.2888-5_2907del	c.3025_3028+11del
c.2888-36_3011del	c.2888-21_2913del	c.2888-5_2909del	c.3025_3028+15del
c.2888-35_2888-27del	c.2888-20_2888-9del	c.2888-5_2944del	c.3026_3028+11del
c.2888-35_2888-20del	c.2888-20_2888-4del	c.2888-4_2910del	c.3027_3028+2del
c.2888-35_2888-17del	c.2888-20_2888-3del	c.2888-2del	c.3027_3028+3del
c.2888-35_2888-1del	c.2888-20_2888-2del	c.2888-2A>G	c.3027_3028+4del
c.2888-35_2888del	c.2888-20_2888-1del	c.2888-2_2915del	c.3027_3028+7del
c.2888-35_3011del	c.2888-20_2898-2del	c.2888-1G>C	c.3028del
c.2888-33_2888-12del	c.2888-20_2899del	c.2888-1G>A	c.3028G>A
c.2888-33_2888-7delinsTTAAAACTG	c.2888-20_2913del	c.2888-1G>T	c.3028G>C
c.2888-32_2888-13del	c.2888-20_2939del	c.2888_2919del	c.3028G>T
c.2888-32_2888-11del	c.2888-20_3028+1133del	c.2903_3028+67del	c.3028_3028+1del
c.2888-32_2889del	c.2888-19_2888-13delinsAAA	c.2907_3028+49del	c.3028_3028+3delinsCC
c.2888-32_2967del	c.2888-19_2888-10del	c.2920_3028+10del	c.3028_3028+5del
c.2888-31_2888-15del	c.2888-19_2888-9del	c.2931_3028+2731del	c.3028_3028+16del
c.2888-31_2888-15delinsA	c.2888-19_2888-8del	c.2938_3028+146del	c.3028+1del
c.2888-31_2888-13del	c.2888-19_2888-4del	c.2983_3028del	c.3028+1G>A
c.2888-31_2888-10delinsGTT	c.2888-19_2888-3del	c.2990_3019del	c.3028+1G>C
c.2888-31_2891del	c.2888-19_2888-2del	c.2995_3028+221del	c.3028+1G>T
c.2888-30_2888-26delinsG	c.2888-19_2888-1del	c.2998_3028+6del	c.3028+1_3028+2 del
c.2888-30_2888-5del	c.2888-19_2909del	c.3000_3028+9del	c.3028+1_3028+3delinsTT
c.2888-30_2888-3del	c.2888-19_2921del	c.3001_3021del	c.3028+1_3028+4del
c.2888-30_2895del	c.2888-18_2888-9del	c.3001_3028del	c.3028+1_3028+9 del

(Continued)

Table A1. (Continued)

c.2888-30_2898del	c.2888-18_2888-8del	c.3003_3028+6del	c.3028+1_3028+13del
c.2888-30_2907del	c.2888-18_2888-7del	c.3004_3028+3del	c.3028+2T>A
c.2888-29_2888-28delinsGG	c.2888-18_2888-5del	c.3004_3028+17del	c.3028+2T>C
c.2888-29_2888-10del	c.2888-18_2888-4del	c.3005_3028+1del	c.3028+2T>G
c.2888-29_2891del	c.2888-18_2888-2del	c.3005_3028+11del	c.3028+2_3028+3delinsGT
c.2888-29_2920del	c.2888-18_2888-1del	c.3007_3028+13del	c.3028+2_3028+4delinsACC
c.2888-29_3028+691del	c.2888-18_2892del	c.3008_3028+7del	c.3028+2_3028+10del
c.2888-28_2888-16del	c.2888-18_2953del	c.3009_3028+7del	c.3028+3A>C
c.2888-28_2888-14del	c.2888-17_2888-8del	c.3009_3028+10del	c.3028+3A>G
c.2888-28_2888-14delinsA	c.2888-17_2888-7del	c.3009_3028+13del	c.3028+3A>T
c.2888-28_2888-9del	c.2888-17_2888-4del	c.3010_3028+8del	c.3028+3del
c.2888-28_2888-7del	c.2888-17_2888-3del	c.3010_3028+1318del	c.3028+3_3028+7del
c.2888-28_2888-6del	c.2888-17_2888-2del	c.3012_3027del	
c.2888-28_2888-5del	c.2888-17_2888-1del	c.3012_3028+4del	