Peer Review File

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Reviewer #1

The article represents a very important contribution for further improving of implementation of molecular testing and targeted therapy by reflecting the real-world status quo and by identifying different barriers and limitations.

Comments to the title:

The word "Genetic" is mostly used in the context of testing that look for certain inherited gene alterations (germline). The word "Genomic" refers to testing tumor issue (and/or liquid biopsy, e.g., blood). So, to not make the readers confused, it will be more relevant to use the word "genomic" testing, or biomarker testing, or molecular testing.

Furthermore, there is no standard molecular testing for SCLC, so you may precise the title to "NSCLC" instead of "lung cancer", as the testing does not apply for all types of lung cancer.

Reply: We thank the Reviewer for the comments. It was revised throughout the manuscript.

Changes in the Text: Genomic testing and targeted therapy of non-small cells lung cancer in China: A nationwide survey of physicians and clinical pathologists. **(**Line 1)

Line 37: "…, and C-ros oncogene 1 (ROS-1) mutations testing."

First, to maintain a unified naming convention of gene, you do not need use prefix "c" here, which stands for "cellular" in this context. It is correct to write ROS proto-oncogene 1, receptor tyrosine kinase, or Reactive Oxygen Species 1 (ROS-1) gene.

Second – please remove the word "mutations" in the same line, as ALK and ROS1 are not investigated for mutations, but fusions. You can just use "testing".

Reply: We thank the Reviewer for the comments. It was revised throughout the manuscript.

Changes in the Text: Clinical pathologists reported capability of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and reactive oxygen species 1 (ROS-1) testing as 95.3%, 94.7%, and 84.7%, respectively. (Line 31)

Line 43: lack of space between "ROS-1" and "rearrangement".

Reply: We are sorry for the typo. It was revised.

Changes in the Text: Testing for EGFR mutation was recommended by physicians most often, followed by ALK and ROS-1 rearrangement. (Line 37)

Line 70: instead of "oncogenic driver mutations" use "oncogenic driver alterations" as you also refer to translocations in ALK- and ROS1 genes.

Reply: We thank the Reviewer for the comments. It was revised accordingly.

Changes in the Text: Upon the discovery of several oncogenic driver alterations, treatment of NSCLC has shifted to targeted therapy. **(**Line 57)

Line 79: You can with advantage citate newer NCCN recommendation for testing: National Comprehensive Cancer Network. Non-small lung cancer (version 3.2023). Guidelines Detail (nccn.org)

Reply: We appreciate your guidance to reference the most current guidelines in our study. In response to your suggestion, we have updated the text to include the latest NCCN recommendations.

Changes in the Text: Following the identification of multiple oncogenic driver alterations, as delineated in the National Comprehensive Cancer Network (NCCN) guidelines, the treatment paradigm for NSCLC has increasingly shifted towards targeted therapies (1). Alterations with currently approved targeted therapies include EGFR mutations, ALK rearrangements, ROS-1 rearrangements, BRAF mutations, and neurotrophic tropomyosin-receptor kinase (NTRK) gene fusions (2). **(**Line 69)

Line 80: please don to mix mutations and translocations. Instead of "mutations" use "alterations" as you mention both mutation and translocations, which are completely different molecular events.

Reply: We thank the Reviewer for the comments. It was revised throughout the manuscript.

Changes in the Text: Alterations with currently approved for targeted therapies include EGFR mutations, ALK rearrangements, ROS-1 rearrangements, BRAF mutations, and NTRK gene fusions. **(**Line 72)

Line 88: "not been reported before". However, there is previously published paper about testing up to 2019: Li, Wenbin et al. "Trends in Molecular Testing of Lung Cancer in Mainland People's Republic of China Over the Decade 2010 to 2019." JTO clinical and research reports vol. 2,4 100163. 11 Mar. 2021, doi:10.1016/j.jtocrr.2021.100163, and you refer to this artciel and discuss how the trends have been changed.

Reply: We thank the Reviewer for directing our attention to the study by Li et al.,(3) which provides valuable insights into the trends in molecular testing of lung cancer in mainland China over the decade from 2010 to 2019. Our study acknowledges the foundational work done by Li et al., and builds upon it by specifically focusing on the perception of genetic testing and targeted therapy for NSCLC among clinical pathologists and physicians in China. While Li et al.'s research extensively covers the historical progression and geographical distribution of molecular testing capabilities, our study delves into the current state of practice, assessing the differences in perception between pathologists and physicians regarding the capability of their institutions to conduct these tests, as well as the actual application and impact of these tests in clinical treatment as of 2020. Hence, our findings provide a novel perspective on the application of genetic testing and its influence on treatment decisions in the recent context, complementing the historical overview provided by the previous study.

Changes in the Text: While previous studies, such as the one by Li et al.,(3) have detailed the historical progression and distribution of genomic testing for LC in China,

there has been limited reporting on the contemporary rate of genomic testing for specific alterations in NSCLC, the differential perceptions of pathologists and physicians regarding these tests, and the direct impact of test results on clinical treatment decisions. Our study addresses this gap by conducting a comprehensive questionnaire survey aimed at evaluating the current understanding of NSCLC genomic testing among pathology and clinical departments, assessing the detection capabilities of hospitals for NSCLC genomic alterations, exploring clinical recommendations for such testing, and examining the specifics of targeted therapy administration in NSCLC patients. (Line 79)

Line 135-136: Table. 1 You can explain for the readers what it means in the China context Tertiary hospital: First-tier cities, second-tier cities, and third-tier cities, thank you.

Reply: We thank the reviewer for highlighting the need for clarity regarding the categorization of hospitals in the context of first, second, and third-tier cities in China. In China, hospitals are often categorized based on the tier of the city in which they are located:

First-Tier Cities: This category includes Beijing, Shanghai, and Guangzhou. These cities represent the most economically and medically developed areas in China, often featuring advanced healthcare infrastructure and resources.

Second-Tier Cities: These are typically provincial capitals, such as Hangzhou, Chengdu, Wuhan, etc. Second-tier cities generally have considerable medical resources and are well-developed, though they may not match the scale and sophistication found in first-tier cities.

Third-Tier Cities: This category encompasses areas that are not included in the first and second tiers. Third-tier cities generally have less developed healthcare infrastructure compared to the higher-tier cities.

Changes in the Text: In this study, the classification of hospitals was based on the tier system of cities in China. First-tier cities, including Beijing, Shanghai, and Guangzhou, represent the most medically advanced and economically prosperous

regions. Second-tier cities, such as provincial capitals like Hangzhou, Chengdu, and Wuhan, offer considerable but varied medical resources. Third-tier cities encompass all other areas, typically with less developed healthcare infrastructure. (Line 118)

Line 184-185: "Feedback from interviewed clinicians, the main reasons for sending out specimens were…", please rephrase the sentence to be understandable, f.e., The Feedback form interviewed clinicians revealed that…"

Reply: We thank the Reviewer for the comments. It was revised accordingly.

Changes in the Text: Feedback obtained from the clinicians we interviewed revealed that the primary reasons for sending out specimens included that the pathology department of the hospital cannot perform the testing method or technique (78.9%), patient chose to be sent out of the hospital (26.4%), preferential price (17.7%) and re-testing (12.2%). (Line 185)

Line 228: "Personalized therapy of LC is based on the genetic testing" please rephrase. LC should be changed to NSCLC, as personalized therapy only applies to NSCLC, not the entire group of LC. Furthermore, "genetic testing" as mentioned before is not optimal term here, as it refers to germline alterations. The word "genomic testing" or "molecular testing" are appropriate here.

Reply: We thank the Reviewer for the comments. It was revised accordingly.

Changes in the Text: Personalized therapy of NSCLC is based on the genomic testing, which is necessary to guide optimal treatment. (Line 229)

Line 245: "…while tissue biopsy is the least effective…". Can you explain why is that? Is it because the biopsies are insufficient?

Reply: We appreciate your query, which prompted us to refine our explanation. We have revised the sentence to clarify that the lesser effectiveness of tissue biopsy, compared to liquid biopsy, is largely due to its longer turnaround time. This is supported by the study by Raez et al.,(4) which found that liquid biopsy NGS returned results faster than tissue biopsy. In the context of our study, this time factor is critical, as

physicians often seek to obtain results within a much shorter timeframe to make timely treatment decisions. This revision is now reflected in the manuscript.

Changes in the Text: In our study, when considering long-term costs and effects, liquid biopsy was reported as the most effective and most costly strategy, while tissue biopsy was the least effective and least costly. This is primarily attributed to the longer turnaround time for tissue biopsy results, with liquid biopsy NGS returning results faster, as indicated by Raez et al.(4) This delay in obtaining tissue biopsy results can be crucial, particularly when physicians aim to receive results within a shorter timeframe to expedite treatment decisions. (Line 244)

Line248-250: "The key reason for the differences in perception between clinicians and pathologists as to the detection ability of pathology departments described above is the lack of communication between clinicians and pathologists". Please re-phrase to make this very important sentence understandable", e.g. "The key reason… is…"

Reply: We thank the reviewer for highlighting the need to clarify an important aspect of our study. We have revised the sentence.

Changes in the Text: The primary factor contributing to the observed disparities in perception regarding the detection capabilities of pathology departments between clinicians and pathologists is attributed to insufficient communication between these two groups. (Line 253)

Line 259: "One of the approaches to the low rate of genetic testing, proposed in the literature, is…". Please re-phrase the sentence, as is not understandable.

Reply: We thank the reviewer for pointing out the need for clearer expression in our manuscript. We have rephrased the sentence.

Changes in the Text: A proposed solution in the literature to address the low rate of genomic testing is the automatic initiation of genomic testing by pathologists immediately following the histological diagnosis of advanced NSCLC with adenocarcinoma. (Line 264)

Line 262: "… college of American pathologists…" change to "College of American Pathologists" as it is the institutional name.

Reply: We thank the Reviewer for the comments. It was revised.

Changes in the Text: Updated genomic testing guidelines from the College of American Pathologists… (Line 266)

Line 282: "…in cases of rare mutations" change to "in cases of rare alterations". You can also underline in the discussion that (line 201) 38.6% of physicians respond with "No understanding of genetic testing". What will be your suggestion to improve it?

Reply: We thank the reviewer for their insightful suggestions. In accordance with your recommendation, we have changed "rare mutations" to "rare alterations" for accuracy. Furthermore, addressing your concern raised in line 201 about the 38.6% of physicians with no understanding of genetic testing, we propose enhancing awareness through education. We suggest the dissemination of comprehensive information about NSCLC genomic testing to patients and their families, aiming to improve both awareness and testing compliance.

Changes in the Text: To address the significant percentage of physicians lacking understanding in genomic testing, we advocate for the widespread dissemination of educational materials on NSCLC genomic testing to patients and their families. This approach aims not only to enhance the awareness of patients and their families but also to potentially improve compliance with testing recommendations, thereby bridging the knowledge gap and facilitating more informed clinical decisions. (Line 286)

Line 312: "…especially for ROS1 fusion". You can also extend the need for testing for other biomarkers according to NCCN (ERBB2, BRAF, KRAS, RET, NTRK, NRG1, MET) as you mentioned in the introduction.

Reply: We thank the reviewer for your suggestion to broaden the scope of our conclusion regarding genomic testing needs. We have revised the sentence to include a broader range of biomarkers as outlined in the NCCN guidelines, thereby aligning our

conclusion more closely with the comprehensive approach to genomic testing emphasized in the introduction of our paper.

Changes in the Text: In conclusion, while there is a need for overall enhancement in the genomic testing landscape for NSCLC patients in China, it is particularly crucial for biomarkers like ROS1 fusion, along with others specified in the NCCN guidelines such as HER2, BRAF, KRAS, RET, NTRK, NRG1, and MET. (Line 325)

In discussion you may also point out other factors beyond further education and improved co-operation between clinicians and pathologist, as e.g., a role of patients involvement (patients advocacy).

Reply: We appreciate your suggestion to include the role of patient involvement in our discussion. We have added a section highlighting the significance of patient advocacy and experience sharing in genomic testing and targeted therapy for NSCLC. This addition underscores the value of patient engagement in improving treatment outcomes and confidence in care.

Changes in the Text: To complement educational efforts and enhanced collaboration between clinicians and pathologists, we also recognize the importance of patient involvement and advocacy. Actively engaging patients in sharing their experiences with genomic testing and targeted therapy can significantly bolster patient confidence and involvement in their own care. Such patient-centric approaches can be pivotal in enhancing the overall effectiveness of NSCLC treatment strategies. **(**Line 312)

Reviewer #2

The article is basically okay though there are some tense issues. Please check on the comments and suggestions below for further improving the article.

Some Suggestions / Comments:

Line 32: "with 150 clinical …"
Line 40: "performing the testing"
Line 41: "which reported" => "as reported"
Line 57 point 1: "even though" => "there was"
Line 57 point 4: "require improvement in physician awareness."
Line 68: "are still very close" => "are still very high" (please review the word choice)

Line 78-79: please check if the abbreviations like "BRAF", "KRAS", etc. can be defined first
Line 80: delete the "for" before "targeted therapies"
Line 86: "described above" => "the aforesaid"
Line 100: "or with more than…"
Line 103: "the questionnaire"
Line 109: "included" (simple past tense for Methods and Results presentation)
Line 122: "met" (simple past tense for Methods and Results presentation)
Line 130: "8,000" (please use this format for all the numbers across the whole paper for easier reading)
Line 131: "As the doctors" => "As some doctors"
Line 137: no "s" for "pathologist" after "each"
Line 138, 139: "had"; "did not have" (simple past tense for Methods and Results presentation)
Line 147: "was the most frequent testing regardless if it was from the thoracic surgery department…" (presentation)
Line 160, 163, 171, 247: "believed" (simple past tense for Methods and Results presentation)
Line 161, 167, 171: "was" (simple past tense for Methods and Results presentation)
Line 168, 170: "were" (simple past tense for Methods and Results presentation; please check for the rest of the Results part for the tense usage)
Line 235-236: "are" => "were" (simple past tense for Methods and Results presentation)
Line 236-237: "needed were essentially…" (simple past tense for Methods and Results presentation)
Line 241: "is" => "was" (simple past tense for Methods and Results presentation
Line 256: "the lack of"; "has still not completely solved"
Line 271: "the already obtained…"
Line 275: add a full stop before "In the face of"
Line 266: add a comma after "China"
Line 288-289: "was detected"; "did not follow" (simple past tense for Methods and Results presentation)
Line 295: "even though there was a higher proportion…" (verb usage)
Line 306: "should help to assess" => "would help assess"
Reply: We thank the Editor for the comments. We have revised the manuscript accordingly. Please kindly review.