Peer Review File

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Reviewer A

Overall, an informative review which summarizes the development of CDx in recent years. The author did well in elaborating the history while also addressing clinical development. The review covers several topics, including diagnostic platforms used for CDx testing, involved drugs and biomarkers.
It was also able to present the versatility of the biomarkers studied, which have been further explored in recent years. These include important points such as MSI and MMR, but also the trend towards NGS-based platforms.
However, when looking at CDx over the last 25 years, it should be considered that there has been a global evolution in the introduction of CDx testing (US, EU, Japan, Canada, Australia). Alternatively, it should be made clearer (abstract/title) that this is a review focusing on the CDx development in the US.

Response: I agree, the introduction of CDx is a global event, and references have now been made to a number of other regulatory bodies. Furthermore, it is now mentioned in the abstract that the focus of the article is on the United States.

Line 47/48: Misleading wording about the terming of CDx, the test for the detection of the biomarker is relevant.

Response: The sentence has been rephrased.

Line 97: Maybe refer to the FDA drug label/prescription information. This makes it clear that the CDx test is mandatory prior to treatment.

Response: A reference has now been made to the FDA's full prescription information for trastuzumab.

Line 123-125: Please add a suitable reference for the statement.

Response: The sentence has been rephrased and a reference has been added. Furthermore, the opinion of the German Federal Institute for Drugs and Medical Devices on the same subject has been included, and an additional reference has been added.

Line 136: "other regulatory bodies" Please note that the introduction of CDx is a global phenomenon. CDx were introduced by Japanese PMDA, Canadian HCSC and Australian TGA. The statement would be more balanced by adding a variety of countries/regulatory bodies in addition to Europe and the US.

Response: I completely agree with this point of view and a number of other regulatory agencies are now mentioned, as well as the implementation of the IVDR in Europe. Several additional references have been included.

Line 167: Is the proportion for in situ hybridization (ISH) composed of FISH and CISH?

Response: Yes, ISH includes both FISH and CISH, and a sentence has now been included to explain this.

Line 210: "less than 100 patients" please specify the reference where this number is originated from (for example the FDA document). Does this number reflect a disease-specific cohort in a pivotal study?

Response: References are now made to the full prescribing information for the drugs mentioned, and the sentence has been rephrased.

Line 236: “absence of CDx assay”. What is meant by "Absence"? With dabrefenib, for example (reference), no CDx test is provided in the drug label, only an "FDA approved test". This should not lead to problems, as no CDx is required.

Response: This sentence has been revised accordingly. In the FDA full prescribing information for dabrafenib section 1, Indication and Usage, it is mention for patients with metastatic melanoma or NSCLC that testing for BRAF mutation should be performed with a FDA-approved test: Furthermore, in section 2.1, Patient Selection, there is a cross-reference to http://www.fda.gov/CompanionDiagnostics.

Suggestion for displaying the tables: Currently, the data in the table are arranged alphabetically by biomarker. I suggest arranging them in the first column of the table, or to arrange the drugs alphabetically. It is easier to understand if the first column is arranged alphabetically.

Response: Based on the suggestion, the tables have been rearranged.

Reviewer B

I only have minor comments, for consideration.

-The article offers an exclusive view of 1 Regulatory region which is the purpose of the article, however for the reader, the article could benefit of a mention (a glimpse) to the approach for approval by different regulatory regions, for completeness.

Response: I agree, the introduction of CDx is global, and several other regulatory bodies have now been mentioned in the “Companion diagnostic” paragraph.

-It is noted the Reference to the European regulation on the IVDR is included, further link to relevant articles as developed in Europe may be included, see below:

1. Pignatti, F. et al. Cancer drug development and the evolving regulatory framework for companion diagnostics in the European union. Clin. Cancer Res. 20, 1458–1468 (2014). View CAS PubMed Web of Science® Google Scholar

2. -Biomarker−Driven Developments in the Context of the New Regulatory Framework for Companion Diagnostics in the European Union - Verbaanderd - 2023 - Clinical Pharmacology & Therapeutics - Wiley Online Library

Response: The implementation of the IVDR is now mentioned in the manuscript, and both Pignatti and Verbaanderd articles have been included as references.

-On tables 1, 2, 3 description: reference is made to the companion diagnostics biomarkers, however it should refer better to the related biomarkers and not the term companion diagnostic as there is an implicit reference to the assay that however is not mentioned in the table.

Response: The table legends have been changed according to the recommendations.

-On Figure 3, should a reflection be included on the fact that the trend observed is due to the way regulatory

submissions for approval are submitted e.g. linked to more targeted, smaller trials? You establish the link already elsewhere in the document.

Response: Thank you for this comment. A sentence linking the development of CDx to the development of targeted oncological drugs has been included.

This is a very informative and comprehensive paper which captures some of the challenges that at least I have come across in relation to CDx; once published, I will share it to the CDx expert group at The European Medicines Agency, for information purposes.

Response: Thank you very much for the positive feedback, and I am very pleased to learn that you find the article informative, and it is worth sharing with your colleagues at The European Medicines Agency.

Reviewer C

Some of the wording is confusing and I must admit that I have recently read numerous perspectives, and specific commentaries, reviews and/or position papers with very unique and novel points regarding CDX.
PMID: 37663648
PMID: 37520706
PMID: 37331786
PMID: 36338524
The abstract was not able to convey the novelty the authors are providing.

Is there a specific novel aspect?

Response: Thank you for the suggested publications on novel points regarding CDx. Several of the suggested publications have been included as references. Furthermore, the paragraph "Future trends and concluding remarks" has been updated with regard to imaging CDx, liquid biopsy assays, and digital pathology. When it comes to the future CDx's I describe the integration of data from the proteome and the genome in what the NCI call "proteogenomics." Furthermore, it should be noted that the main intention of this manuscript is to describe the past 25 years of evolution within CDx. Additionally, the manuscript has been proofread.