# How current assay approval policies are leading to unintended imprecision medicine

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Pathologists are responsible for selecting the assays for the optimal identification of patients for targeted therapy. The current paradigm of regulatory assay approval is that when a clinical trial involving a drug and a biomarker, using a specific assay to identify patients that might respond to the drug, meets its endpoint, the assay is approved concomitantly as a companion diagnostic. Private health insurance bodies or public health systems then decide on reimbursement of the assay when they decide on the reimbursement of the drug. Use of US Food and Drug Administration (FDA)-approved assays is obligatory in some countries, like the USA and Japan, to gain access to the drug. In the EU, the use of an FDA-approved assay is not mandatory to gain access to the drug, as long as the laboratory-developed test or assay that is used is validated.

Thresholds for defining a positive biomarker in a clinical trial, and what constitutes a positive biomarker, are not standardised. Moreover, companion assays are co-developed with a drug, as determined by the pharmaceutical company in collaboration with the company contracted to produce the assay, without regard to the other assays being developed for the same biomarker. For example, PD-L1 assay kits are approved by the FDA in 15 different cancer types but the PD-L1 staining patterns, scoring methods, and positivity thresholds are different in almost all of these cancer types. Moreover, the various assays and scoring systems are not equivalent, despite being matched to the same specific drug. There are at least five non-equivalent assays for PD-L1, each with its own scoring system and tumour site indications.

Absence of assay standardisation is an emerging issue for triple-negative breast cancer. In 2019, considering the results of the IMpassion130 trial, the FDA approved the Ventana PD-L1 (SP142) assay (Ventana Medical Systems, Tucson, AZ, USA) and cut-point (1% of tumour-infiltrating immune cells) to assess PD-L1 in patients with triple-negative breast cancer treated with atezolizumab.[1] However, following the Keynote 355 breast cancer trial,[2] the results of which were publicised in 2020, investigating pembrolizumab in the same patient population, the FDA is likely to approve the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) and its combined positivity score-scoring system to assess PD-L1. Using more than one assay for the same biomarker is problematic because the assays have different positive prevalence rates. In the IMpassion130 trial, 46% of patients with triple-negative breast cancer were deemed to be positive using the Ventana PD-L1 (SP142) assay; when using other assays (eg, the PD-L1 IHC 22C3 pharmDx assay) in the same patients, the PD-L1 positive prevalence increased to nearly 80%.[3] The cause of these inconsistencies is multifactorial and includes reproducibility issues and variable antibody and assay sensitivity, even when different assays use the same antibody.[4-6] One issue is the balance of risk, costs, and benefit. If treatment recommendations differ depending on the assay that is used, it is difficult for health-care providers to reliably analyse the cost-effectiveness for reimbursement of that particular treatment. Costs are arguably even more important in low-income and middle-income countries. Some private insurance companies or governments insist on the use of FDA-approved assays, which are more expensive than laboratory-developed tests. A concerning situation is if patients underwent unnecessary toxicity and extra costs due to potentially false-positive tests. However, lower sensitivity of an assay, with potentially false-negative results, could lead to fewer patients receiving therapy and benefit. Some oncologists might prefer their pathologist to use an FDA-approved assay, despite being unaware of the analytical validity of the assay and the fact that many laboratory-developed tests can perform as well as FDA-approved companion diagnostics.[7] Others might prefer an assay with a higher positive prevalence to identify more patients that can be treated.

Different assays, different platforms, different positivity thresholds, and a divergent international approach to reimbursement of these assays suggest that patients are not well served by the current system. Industry, regulatory agencies, governments, clinicians, and patients also need to be aware that a positive phase 3 trial does not guarantee consistency, reproducibility, and practicality of the biomarker-specific assay used in

### *Panel:* Solutions to improve the current assay approval pathway

- Industry should be mandated to do concordance studies with other similar assays or standardised controls before a drug is approved
- Industry should support, in concert with all stakeholders, relabelling or revising approved companion diagnostics if evidence exists that the labelling might lead to uncertainty in the identification of patients for treatments
- Industry should support, in concert with all stakeholders, relabelling or revising of the companion diagnostics if equivalent clinical validity has been shown with other biomarkers or standards, providing access to clinical trial tissues to validate other assays
- Industry, when considering the incorporation of assays in their trials, should communicate and share assay information when using an assay that identifies the same molecule (eg, epitope, antigen, DNA, RNA) as in other competitive trials—eg, method information related to the binding sites of the antibodies used in the companion diagnostic assay should be made public, even if this information is commercially sensitive
- Pathways for regulatory acceptance of other assays that are equivalent, but less expensive and easier to implement in daily practice, should be developed by governments and regulatory agencies, ideally before a drug is labelled together with a companion diagnostic
- Early engagement by all stakeholders in external quality control schemes to allow rapid development of guidelines and quality standards is essential, preferably before an assay is approved by the regulatory agencies
- Clinical practice guidelines developed by professional organisations like the American Society of Clinical Oncology and the European Society for Medical Oncology should endorse not just a companion diagnostic assay used in the trial, but any rigorously and technically validated equivalent laboratory assays that can define essentially the same population as the companion diagnostic
- Regulators should require data confirmation of the analytical validity of the companion diagnostic in the distributed setting in which it would be applied, at a level of rigor similar to that required to show efficacy of the drug in question

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the trial. Furthermore, the use of a suboptimal assay might lead to inconsistent trial outcomes when used in different trials investigating the same drug in the same patient population leaving, for example, the best method to select patients for immunotherapy still uncertain.

We propose solutions to industry (pharmaceuticals and diagnostics), academia, patients, governments, and regulatory agencies (panel) who currently hold the keys to resolving the issues outlined here. The current assay approval pathway should be updated to reflect current realities, including mandating a detailed assessment of the analytical validity of an assay before it is considered as a companion diagnostic.

Although PD-L1 is the latest diagnostic challenge, it is neither the first nor will it be the last such challenge to face the community unless focused efforts in a partnership between all stakeholders are directed towards standardisation of assay development for both current and future applications.

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