Anonymous – Response 2

CDx identification guide
I think there needs to be a focus on what constitutes "standard of care" Australian testing, and who makes the decision about what is standard of care. I am a genetic pathologist, and I absolutely view tumour testing for variants in a single gene (like BRAF, example given on p11) or multiple genes (case study 3, p15) as standard of care testing when carried out by a NATA/RCPA accredited laboratory. Tests of tumours for genetics are performed in many accredited labs in Australia, and have been for at least 15 years. I would strongly object to these tests being described as "novel", or subject to "high variability" or "important heterogeneity", as in the box on the bottom right of the guide flow-chart. Therefore, for these two examples pertinent to my scope of practice, I would answer the flow chart as follows: Yes, No, Yes, Yes --> No CDx testing required. If the concept is that a test for BRAF V600E variants now needs to undergo bridging studies/retesting of (now unavailable) clinical trial samples, then BRAF testing in Australia will cease overnight. This would have a dire impact on access of patients to testing. Similarly, inaccurately defining NGS panel testing as "not standard of care" will stifle access to new therapies. Many genetic tests are in-house IVDs; there are relatively few manufacturer-registered IVDs. It is often impossible for individual laboratories to acquire samples which were tested in a clinical trial (these are often exhauseted). If the clinical trial assay was performed overseas, which is typically the case, it is often equally difficult to perform bridging studies, because the individual pathology laboratory has to somehow access the clinical trial assay, and pay for it to be carried out on a large number of samples. This is a large barrier to in-house IVD development, and many laboratories will simply opt out of this process, resulting in a loss of equity of test access to patients. To give a concrete recent example, MSAC application 1783 is for testing tumours with breast cancer for mutations in PIK3CA to determine eligibilty for inavolisib. My laboratory currently has a NATA-accredited tissue PIK3CA assay, which meets in-house IVD NPAAC requirements (and other relevant NPAAC requirements). However, application 1783 cites the INAVO120 trial, which I understand used the Foundation Medicine CGP tests on tissue and plasma DNA (very large, multigene panels). These tests are only available in the US, and cost approx 3000-3500 AUD per test. By comparison, the proposed MBS rebate for single-gene PIK3CA testing is 400 AUD. It would make no sense as a laboratory to spend approx 300 000 dollars to perform bridging studies on 100 specimens, to demonstrate that our already-validated PIK3CA mutation test is valid (which is as noted a standard pathology test). Especially given that this is for a test which will be already marginal to run, with a rebate of 400 dollars. This will simply act as an unnecessary barrier to labs offering testing, which will in turn impair patient access to testing and therapy. I would agree that there are some circumstances where genetic testing is not a "standard pathology test" - e.g. a complex proprietary multi-analyte multigene classifier, where the individual analytes cannot easily be derived from published data (e.g. Oncotype Dx for breast cancer risk). In these cases, using the clinical trial test or comparing to the clinical trial test would be rational, and in the best interests of patient care. However, imposing this requirement for all genetics-related CDxs, even ones detecting variants in one or a few predefined genes (i.e. standard of care testing), is not in patient's best interests, as it will only serve to reduce equity of access with no gains in terms of test analytical/clinical utility - these have been long established for this gene in tumour tissue, under the existing NPAAC/NATA/RCPA framework.

Companion testing plan

I am concerned about the statement that "Australian samples may have to be sent for testing internationally". It is unclear whether this is seen as a long-term solution when there is no Australian test, and who would fund this. Using the example of PIK3CA testing by Foundation Medicine, samples from Australian breast cancer patients *could* all be sent to the US for a 3000 dollar test, but this raises very important questions regarding logistics (who sends the samples? How is the request-report cycle managed?), turn-around time compared with local testing, and cost.

As noted, the proposed MBS rebate for PIK3CA-only testing is 400 dollars, and the trial assay was a 326 gene panel costing approx 3000 AUD. Putting aside the fact that the MBS does not fund testing carried out overseas, there is a gap of 2600 dollars in this case. Who is bearing this cost?

Case studies

I strongly disagree with the classification of an NGS tumour panel (case study 3) as "not standard/mainstream" pathology testing. This type of testing is common in Australia, and it is mainstream/standard of care. Again - who determines what test is standard of care and what is not? I would suggest that there should be consultation with pathology providers/RCPA, as we actually carry out the tests. Is there a plan for such consultation?

Further feedback

It is important to identify when a test used for clinical trials really is not "standard" - e.g. multi-analyte IVDs resulting in a quantitative score with a cut-off determined by an overseas provider (like OncotypeDx).

However, we should not insist on harmonisation with a specific clinical trial assay when the analyte being identified really is standard-of-care - like a tumour tissue test for variants in a small number of genes.

This regulatory guidance as written risks limiting access of Australian patients to new therapies, and compromising patient safety. Examples given for "novel" companion diagnostics are in fact standard-of-care in current practice (BRAF, multi-gene NGS panels). I am sure this is not the intent of the guidance, but I believe this will be the outcome, unless it is re-written with better examples of truly novel IVDs. Clarity also needs to be provided on how it is determined what test is novel and what is standard/mainstream, and which bodie(s) make this determination.