Researchers Develop Decision Matrix to Guide Payors on Clinical, Economic Value of Companion Tests

Jul 23, 2015 | Turna Ray

Premium

NEW YORK (GenomeWeb) – Researchers have developed a decision tool to help payors prioritize the companion diagnostics that require full technological assessments based on a four-step process exploring regulatory status, clinical utility, and clinical and economic value.

Through literature reviews of cost-effectiveness studies and interviews with stakeholders, researchers led by the University of Washington's David Veenstra identified value drivers for companion diagnostics. Based on this, they developed a draft decision support tool, which they piloted with test developers and evidence reviewers at managed care organizations. They then evaluated and improved the tool after testing it out using currently marketed companion tests, and then published a final version of the framework in the *Journal of Managed Care & Specialty Pharmacy*.

"This tool highlights the importance of individual test characteristics … and market-level forces (market penetration and adherence) in determining the value of a companion diagnostic," Veenstra and colleagues wrote in the paper. Because the evidence and market characteristics for a test can change over time, healthcare decision makers can also use this tool to reevaluate tests, they said.

Veenstra previously worked with the Academy of Managed Care Pharmacy (AMCP) to create a submission format that technology developers can use to submit evidence to payors specifically on companion tests. "In part out of that work, and in discussions with payors, it became clear that a lot of them out there weren't quite sure how to approach evaluating companion diagnostics," Veenstra told GenomeWeb.

Companion diagnostics discern patients' differential responses to a treatment and are a critical piece of personalizing treatments. As such, the first step in the four-part process developed by Veenstra, *et al.,* helps evidence reviewers determine whether a test is a CDx. Although seemingly straightforward, payors have muddled prognostic (measuring disease risk) and predictive tests (assessing likelihood of drug response) from an evidence review standpoint.

For example, the Centers for Medicare & Medicaid Services recently asked one of its advisory committees to evaluate the prognostic value of BRAF, KRAS, ALK, EGFR, and KRAS mutations, markers largely known in the literature to be predictive of cancer patients' responses to drugs. Experts have criticized the exercise as a waste of resources.

Although some predictive markers can be prognostic, it is also true that managed care professionals often lack experience evaluating evidence around molecular diagnostics, Veenstra noted, "So, it can be confusing and it's something we're helping people to step through."

Four-step framework

Using the framework outlined in the paper, after determining a test is a CDx in the first step, the reviewer moves on to assess if an evidence review should be prioritized for the diagnostic based on FDA regulatory status, whether results can direct treatment based on available evidence, and if results would impact treatment patterns.

If the CDx passes muster under this second step, then the review considers the test's clinical validity, clinical utility, and analytical performance. Lastly, the reviewer considers the CDx's economic value, evaluating its budget impact, the prevalence of biomarkers it gauges, the cost and effectiveness of the companion drug compared to other treatment options, and test cost. In total, the framework takes the reviewer through 13 questions about the CDx.

To assess how currently marketed companion tests would fare based on this tool, Veenstra and colleagues applied the framework to ALK testing to identify best responders to the non-small cell lung cancer drug Xalkori (crizotinib); HLA-B*5701 testing to predict serious hypersensitivity reactions to the HIV drug Ziagen (abacavir); Oncotype DX to discern which breast cancer patients are low risk for recurrence and can forgo chemotherapy; and pharmacogenetic testing to characterize how patients metabolize the anticoagulant warfarin and guide dosing.

Testing for ALK rearrangements and HLA-B*5701 did best within this framework since ALK testing has been studied as part of the development program for Pfizer's Xalkori and Ziagen sponsor GlaxoSmithKline conducted a randomized controlled trial to assess the effectiveness of HLA-B*5701 screening. The FDA has also approved two ALK companion tests and requires HLA-B*5701 testing in the Ziagen label. Based on these factors and within the framework developed by Veenstra and his colleagues, managed care reviewers would find they wouldn't have to perform an in-depth review of these tests' clinical impact and could prioritize them for evaluation of overall economic value.

"When you have a trial for a drug where the patient population studied is an enriched population, like with Herceptin and HER2 testing, the clinical trial data is in that subset of patients," Veenstra said. "The test and drug are linked and you can't separate the value of those two."

But when the companion test comes after the drug has been on the market, evaluating the value of the CDx gets trickier. Veenstra's group pointed out in the paper that the HLA-B*5701 testing is the only example where a drugmaker has done a randomized controlled trial for a CDx in the post-market setting of a drug. Diagnostics shops marketing FDA-cleared CYP2C19 tests that can be used to guide decisions about antiplatelet treatment have complained that because pharmaceutical sponsors of Plavix (clopidogrel) never supported development of a CDx, their tests have had an uphill battle in terms of adoption and coverage.

Few molecular testing firms can afford to do the extensive studies that Genomic Health has performed on its Oncotype DX test. That diagnostic would move through the CDx assessment framework and end up with a recommendation for a full economic analysis. Genomic Health has shown in multiple studies that the test has predictive value to determine which patients can avoid chemotherapy; the test could have a large budget impact since it gives 20 percent of women actionable results; and it carries a high price tag, the study authors pointed out.

Meanwhle, PGx testing for warfarin based on published evidence would pass muster with regard to clinical validity in this framework, but stumble when it comes to clinical utility, Veenstra's group wrote.

Unlike other more complicated and exhaustive decision support tools for molecular diagnostics available to decision makers, Veenstra and colleagues aimed to develop a systematic framework that was simple and efficient in assessing the value of a CDx in a clinical pathway. "You need something that's pragmatic," Veenstra said. "You don't have two or three days to dig deep into evaluating every test that comes along."

Different perspectives on value

In the coming years, payors will likely have to get very comfortable evaluating the evidence and value of companion tests as more and more of them will be part of personalized treatment paradigms. In 2006, the Personalized Medicine Coalition (PMC) estimated there were 13 such products on the market, and as of 2014, there were more than 100 examples of personalized therapies.

The US Food and Drug Administration lists about a dozen drugs with companion tests on its website; some drugs, like the breast cancer drug Herceptin (trastuzumab), have multiple CDx options. But the agency has also updated the label of 137 treatments with pharmacogenomics information, which in many cases necessitate laboratory tests to identify best responders in the absence of FDA-approved companion diagnostic options.

Since companion diagnostics exist in a complex market amid evolving regulations — where FDA-approved kits exist alongside lab-developed tests of varying capabilities — payors are especially challenged when discerning which tests to cover for beneficiaries and in what clinical context. The very nature of most companion tests — usually intended for small patient subsets — make it difficult for test developers to do the traditional studies (prospective, large randomized controlled trials) payors are used to. "The reality is that the vast majority of [companion tests are] going to have observational data," Veenstra said.

In speaking with both of these groups, Veenstra and colleagues highlighted in the paper how differently these stakeholders think about evidence. Test developers they interviewed complained that payors had overly restrictive evidence criteria, even though companion tests impact medical decisions and are relatively low cost compared to drugs. One test facilitator told researchers, "You could tell [payors] this drug saves lives only if the sun is coming up and they'll ask you, 'How do I know the sun is coming up?' It's observational and all retrospective."

Payors, concerned about the value of a test but also cost containment, disagreed. One expert researchers interviewed said, "There has been great promise for 30

years but companion diagnostics still don't have a lot of impact on clinical practice."

We're really just trying to get that conversation going.

In developing this tool, Veenstra said his group tried to emphasize that it's not so much the level of evidence that determines coverage of a test, but that it's all about the clinical context and patient population within which any given test is used. "We try to emphasize that you can have direct evidence from a randomized controlled trial but you can also have indirect evidence from a variety of different data sources," he said.

Certain tests with data from observational and association studies, and risk/benefit modeling, such as CYP2C19 testing for identifying poor metabolizers of the anti-platelet drug Plavix (clopidogrel), could do well within this decision tool.

Some health systems that have implemented PGx testing for warfarin and clopidogrel have done so in a preemptive fashion, using electronic medical records, in specific clinical contexts, such as for patients presenting to a catheterization lab for CYP2C19 testing. In this way, doctors have access to a patient's genotype information at the time they're prescribing the related drug.

Veenstra noted that if studies show clinicians can't get test results in a timely manner, then it is likely to impact a payor's assessment of a companion test's value. But implementing preemptive testing too broadly and testing those who don't need it could also hurt the value assessment. In the future, broader adoption of much cheaper, next-generation panels could be a paradigm shift for the market, Veenstra observed, but for now, most payors haven't been very receptive to such platforms.

"We're hopeful this can help payors understand how indirect evidence can be useful, as well as help the manufacturers recognize … what's the framework for presenting data to payors in a way that helps them understand its value," Veenstra explained. "We're really just trying to get that conversation going."

Veenstra and colleagues are hoping that industry stakeholders, including healthcare decision makers, payors, drug and testing shops, will begin using the CDx tool. They plan to promote the tool through the National Pharmaceutical Council and University of Washington's communications and alliance development resources. They will also spread the word about the assessment tool to PMC's membership.

"We are already getting very positive feedback from Dx developers and clinical and health economics researchers on the tool," Daryl Pritchard, an author on the paper and PMC's VP of science policy, told GenomeWeb. He acknowledged, though, that getting payors to actually use the tool "is a harder nut to crack."

The researchers used interviews with payors to improve the CDx assessment framework, and these stakeholders "ultimately had a favorable opinion of the tool," Pritchard noted. Veenstra further added that the AMCP may include the CDx assessment tool as part of the resources it provides to support clinical and health economic decision making.