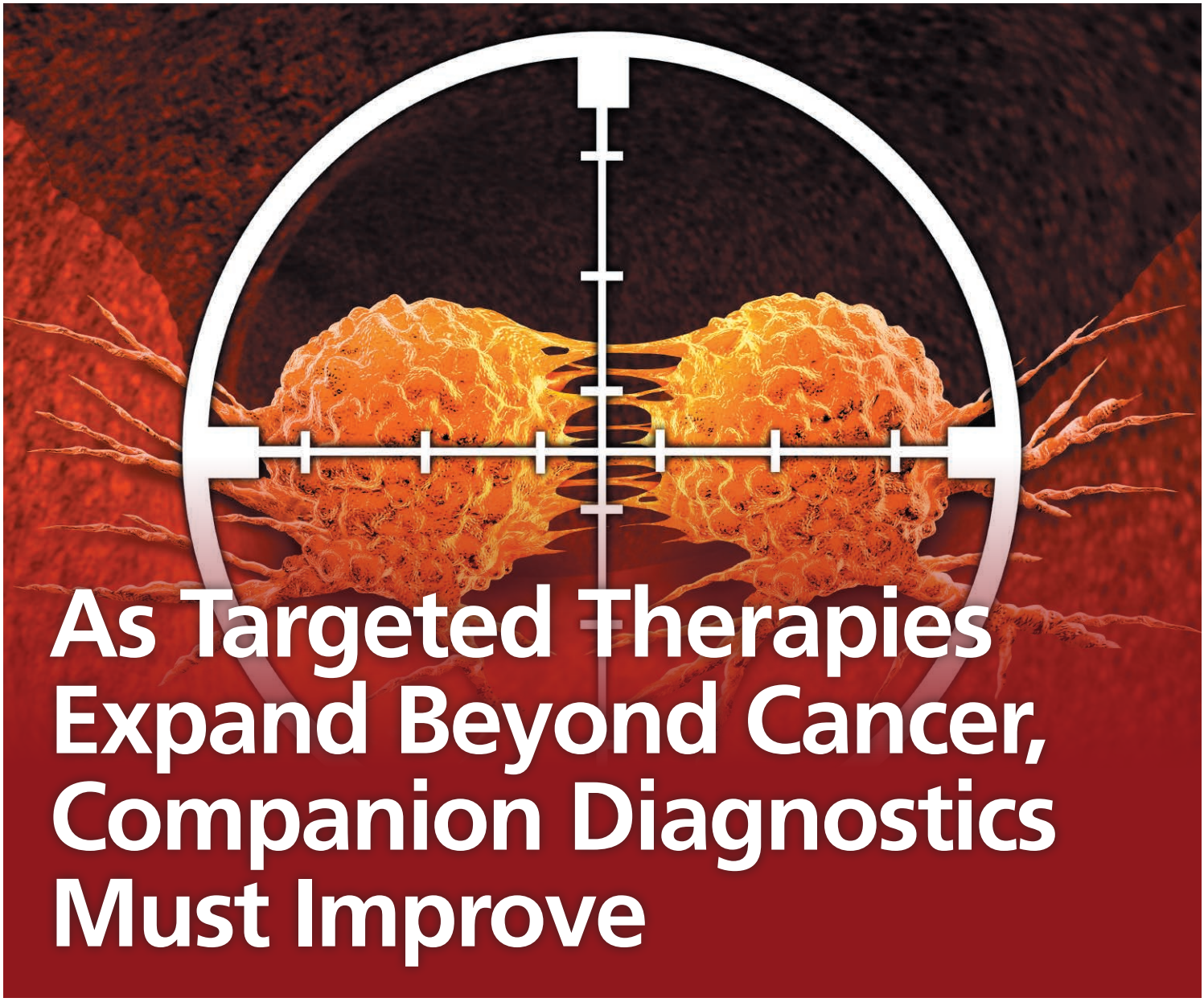

As Targeted Therapies Expand Beyond Cancer, Companion Diagnostics Must Improve

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WHEN SCIENTISTS originally debated the merits of sequencing an entire human genome, proponents argued that genomic data would potentially allow for more precise targeting of therapies to patients. Today, treatments tied to specific genomic variants – and the companion diagnostics needed to identify people with those variants – have transformed patient care.

Targeted therapies and companion diagnostics were first adopted in oncology with great success. Of the 45 companion diagnostics approved by the U.S. Food and Drug Administration so far, all but two were designed for use with cancer treatments.[1] These tests are so important that a recent report estimated the value of the companion diagnostics market at nearly $2 billion in 2019 and predicted that it would reach $9 billion by 2030.[2]

Now, drug discovery scientists are working to extend the benefits of targeted therapies, gene therapies, and other emerging treatments to more disease areas. Patient stratification has made it possible to bring to market drugs that might not meet clinical trial endpoints in a broader patient population; these treatments hinge on the use of companion diagnostics to identify patients most likely to benefit from a therapeutic candidate.

However, some disease areas and genome variants are more challenging to tackle, both in drug discovery and in companion diagnostic development. For example, there is a pressing need for new treatment options for neurological diseases. But detecting and validating target-worthy biomarkers is far more difficult in the brain, where collecting a tissue biopsy sample is not possible and variants tend to be more complex. Liquid biopsy-based methods represent one promising approach to biomarker testing in such conditions, where exosome collection from cerebrospinal fluid may provide a less-invasive yet holistic picture of the disease. On the diagnostic front, it's relatively simple to detect a single nucleotide variant – but many neurological diseases have complex genetic underpinnings that aren't easily detected using conventional molecular techniques such as PCR and Sanger or short-read

next generation sequencing. Sequence variants and repeat length polymorphisms are very difficult to detect in repetitive and CG or AT rich regions, and it is significantly harder to ascertain reliably whether one variant is on the same allele as another variant several kilobases away.

With more advanced companion diagnostics being developed, though, it should be possible for pharmaceutical and biotechnology scientists to develop and commercialize new treatments even for neurological diseases. A new approach in this area illustrates how this might work.

Targeting Huntington's Disease

Huntington's disease – an incurable degenerative condition – is a prime example of a neurological condition crying out for new treatment options. The autosomal dominant disease is caused by an expanded cytosine-adenine-guanine (CAG) triplet repeat in the huntingtin (*HTT*) gene that results in production of mutant HTT protein. Certain single nucleotide variants are associated with the expanded CAG repeat in many patients with HD. Targeting that variant for personalized treatment is a promising concept, but it's made more complicated because the wild type allele must be left intact as the protein it encodes has a number of critical functions in the central nervous system.

The disease-associated CAG repeat expansion in the *HTT* gene occurs on just one allele. Generally, people who have at least 36 of these repeats will develop the disease. If the disease-causing expansion region could be silenced – without affecting the wild type HTT gene on the other allele – it might be possible to alleviate symptoms of the disease.

Scientists are trying to do exactly that with an RNA silencing technology designed to lower the number of disease-causing transcripts while leaving the wild type transcripts intact. Antisense oligonucleotides that selectively target SNPs associated with mutant allele are in clinical development. But to accomplish this, identifying patients with a telltale SNP associated with the CAG repeat expansion is a must – and that is a real technical challenge. Early attempts to do this relied on three different forms of analysis: a PCR test to determine that an individual had at least 36 CAG repeats to meet the requirements of a Huntington's diagnosis; Sanger sequencing to confirm the person had a heterozygous SNP, indicating a likely fit for the targeted treatment; and long-read sequencing to verify that the SNP in question was on the same allele as the CAG repeat expansion to ensure that the person would be eligible for the allele-selective therapy.[3-5]

This serial testing approach is less than ideal. It's expensive, takes a long time, involves multiple technology platforms, and requires a significant amount of processing effort. While it might suffice for a small, early-stage clinical trial, it would be too cumbersome for larger trials or actual clinical use if the therapy were to be approved.

By switching to a different diagnostic platform, scientists were able to generate the information needed with a single straightforward testing kit.[6] This approach makes use of sophisticated amplification technology designed to get through challenging genomic regions, such as repeat expansions, GC-rich elements, and other features that can be challenging for traditional PCR or next-generation sequencing workflows.[7] The same technology underlies a widely used technology for testing for *FMR1* CGG repeat expansions that was recently cleared for use in Fragile X syndrome diagnosis and carrier screening. In the case of Huntington's disease, the technique enabled development of a candidate companion diagnostic that can confirm the repeat expansion size, identify heterozygous SNPs, and generate phasing information in a single workflow.

Why a Partnership Model?

While targeted therapies and companion diagnostics work beautifully in tandem, their development requires vastly different skillsets. Most pharmaceutical and biotech companies prefer to focus on what they do best – bringing new treatments to market – and let a diagnostic developer focus on designing the companion tests.

This partnership approach is especially important as drug developers target more challenging disease areas and more complex genomic variants. Designing an assay for long repetitive sequences, pseudogene discrimination, methylation status, distant variants that may be in cis or in trans, copy number variation, and a long list of other difficult-to-detect biomarkers requires expertise, careful consultation, dedicated technology, and meticulous protocols.

The best diagnostic developers will offer their drug discovery partners not only technical expertise, but also deep experience in commercializing a diagnostic test, getting it through regulatory requirements, and securing reimbursement coverage from payers. The commercial aspect tends to be overlooked, but it is essential since the treatment cannot reach patients without the successful launch of a companion test.

Looking Ahead

The success of targeted therapies in oncology has demonstrated the potential for treatments designed for patients with a specific genetic variant. But as we seek to expand this approach into areas of need beyond cancer, we are coming up against some of the toughest challenges in medicine and trying to solve them with our most advanced, novel, and complex therapeutic designs yet. It makes sense that the companion diagnostics required for these candidate treatments will also have to be cutting-edge – capable of detecting variants that may be elusive for conventional assays and technology platforms. We are confident that the payoff will be worth it as new treatments and diagnostics enable us to make progress toward our goal of realizing the promise of precision medicine. JoPM

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