MRI

The ExoDx™ Prostate Test & mpMRI - A Complementary Approach

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Contents

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Introduction

One of the most widely adopted risk assessment tools employed in prostate cancer (PCa) management is multiparametric magnetic resonance imaging (mpMRI). The EAU, NCCN, and AUA guidelines call for mpMRI utilization in multiple places in the prostate cancer management pathway. Protocols have been implemented, although some have expressed caution about moving too swiftly.[1-3, 80-82] The NCCN Guidelines for Early Detection of Prostate Cancer currently recommend that mpMRI precede biopsy (naïve or prior negative biopsy).

Risk assessment tools including mpMRI all have strengths and limitations. mpMRI limitations include well-known dependencies on reader expertise and therefore variable interpretation, tumor size, multifocality, tissue architecture, process standardization, ethnic and racial availability disparity, potential water resource contamination, and, of course, cost.[4-6] Patient management is best informed when complementary risk assessment methods are appropriately combined to mitigate the limitations of each approach (FIGURE 1).

In this whitepaper, we review the potential strengths and limitations of mpMRI and how biomarkers, specifically the ExoDx Prostate Intelliscore Test (also known as EPI), might be considered, in combination with imaging, to provide the most informed decision-making.[7,8]

Abstract

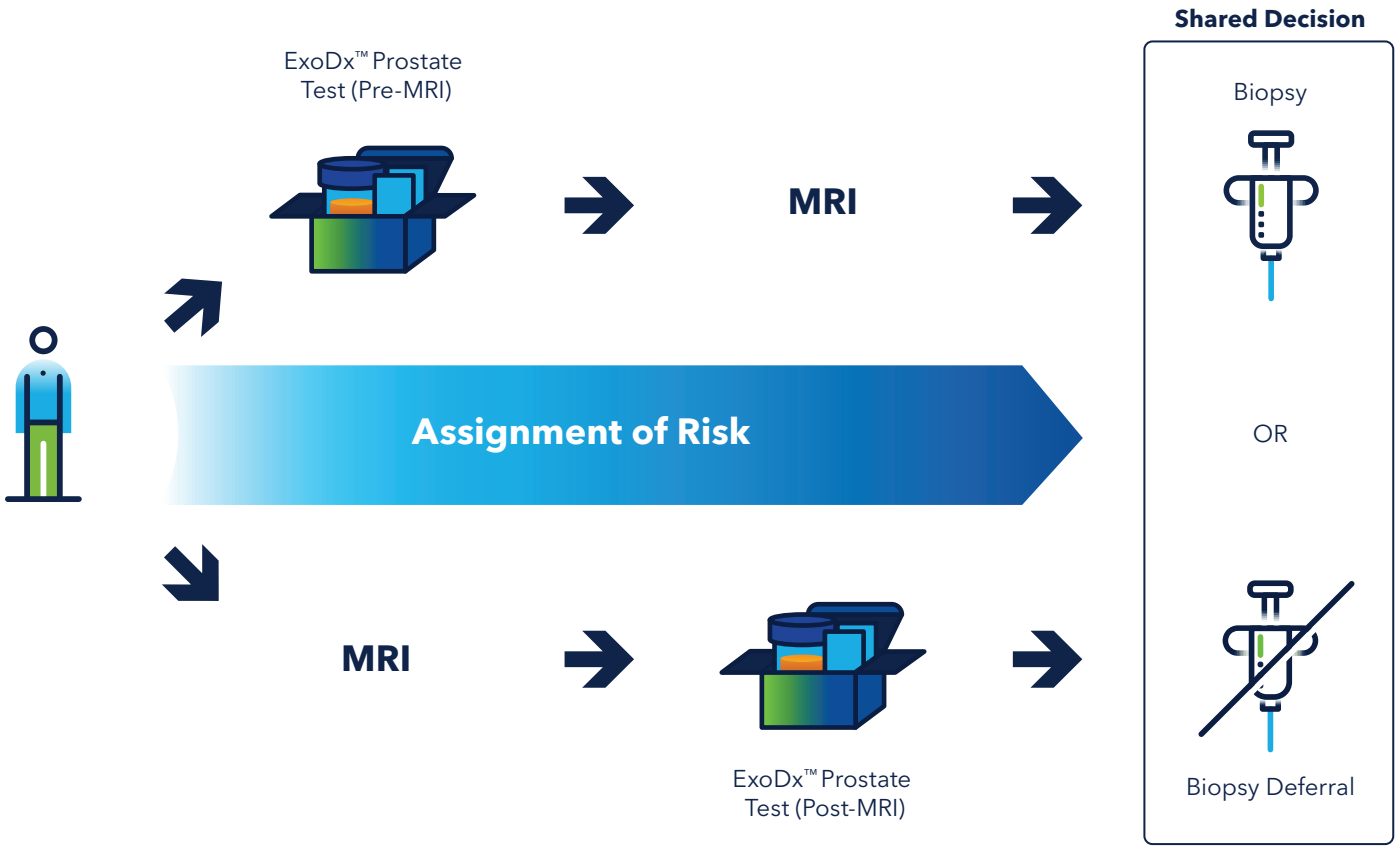


Figure 1 Potential clinical strategies for combining the ExoDx Prostate Test and multiparametric magnetic resonance imaging (mpMRI). Using the ExoDx Test either before or after mpMRI are possible approaches for layered risk assessment and more informed decision-making.[79, 82, 83]

Clinical Challenge

In 2022, 268,490 newly diagnosed prostate cancer cases are projected, and ~34,500 men are expected to die from the disease.[9] However, since the United States Preventative Services Task Force's (USPSTF) decision to alter PSA recommendations, the rate of distant metastasis has increased,[10-12] and there is concern that not doing sufficient biopsies might miss high-grade prostate cancer (HGPCA) (≥GG2). Although prostate biopsy should be employed to find HGPCA, guidelines and much of the medical community look to minimize the detection of low-risk PCa (GG1). Most of these patients will be fine for many years, and if diagnosed with GG1, most will be directed to active surveillance (AS).[1,3]

The clinical question before us is how do we enable the best clinical balance, providing biopsies to men at higher risk for HGPCA while deferring biopsy in men with low risk for HGPCA?

Multiparametric Magnetic Resonance Imaging (mpMRI)

mpMRI is a powerful technology that provides additional insight into which tumors may be clinically significant and where they might reside. Many studies demonstrate the high sensitivity of mpMRI detection for HGPCA, ranging from 82% to 100%, while specificity ranges from 35% to 100%.[13-21] Tumor detection (sensitivity) depends on the type of biopsy performed (TRUS, targeted fusion, targeted visual, etc.). Though still debated, it is widely accepted that mpMRI imaging with biopsy provides either non-inferior or superior detection over TRUS biopsy.[14, 16, 19, 22-24, 25-35] NCCN guidelines highlight the value of mpMRI and the debate about the appropriate mix of image-guided with standard biopsy for tumor detection.[3]

7 Areas for Enhancement

There are acknowledged variations in mpMRI reporting, targeted biopsy methodology, and associated protocols.[51]

1. **Reader Variability/Subjectivity**
   One of the most widely understood mpMRI limitations is reader-dependent variation. In some studies using experienced or 'expert' readers, there are claims of high concordance (78%).[23] Notably, Rosenkrantz *et al* used experienced readers and observed moderate interobserver variability for ≥PIRADS 4 with better agreement in the posterior zone than the transitional zone.[52] Greer *et al* used whole-mount radical prostatectomy (RP) pathology to note that highly experienced readers did better than moderately skilled readers only for ≥PIRADS 4 lesions - not for ≥PIRADS 3 tumors. They suggest that less experienced readers were likelier to score the lesions as PIRADS 3 due to the ambiguity in PIRADS 3 and PIRADS 4 lesions.[4] Standardization is critical to consistent, agreed-upon MRI performance metrics. In a large multinational study spanning 26 sites, the positive predictive value (PPV), the likelihood that a positive result for HGPCA (≥GG2) is truly positive, varied widely from 15%, 39%, and 72% for PIRADS 3, PIRADS 4 and PIRADS 5 respectively.[6] Variation in PPV was likely the result of reader variation, poor targeting, and inconsistent disease prevalence across sites.

2. **Multifocality/Disease Heterogeneity**
   Prostate cancer is often multifocal with different foci displaying both Gleason and genomic heterogeneity.[5,46,47] Unfortunately, mpMRI does not do as good a job detecting multifocal tumors as solitary lesions; multifocality increases the probability of mpMRI-missed tumors[5,34,39] (FIGURE 3). A literature review reveals that 11%-13% of men had HGPCA at a different prostate location than that captured by mpMRI; this raises particular concerns for focal therapies.[48] Stabile *et al* followed fusion biopsy with TRUS biopsy and found 30% HGPCA outside of the index lesion: the Gleason score was equal to or higher than that found in the index lesions. They observed that the likelihood of finding HGPCA outside the MRI-located index lesion grew as the PIRADS score increased: 10% probability for PIRADS 2 and 70% probability for PIRADS 5[34] Studies that incorporate whole-mount radical prostatectomy (RP) are the ultimate pathological ground truth and provide insight into the impact of tumor size and multifocality on mpMRI detection.[5, 39] Bonekamp *et al* observed that even though MRI-detected HGPCA lesions were detected in 97% of men, there were additional ≥PIRADS 3 lesions that were missed in 60% of these cases.[25]

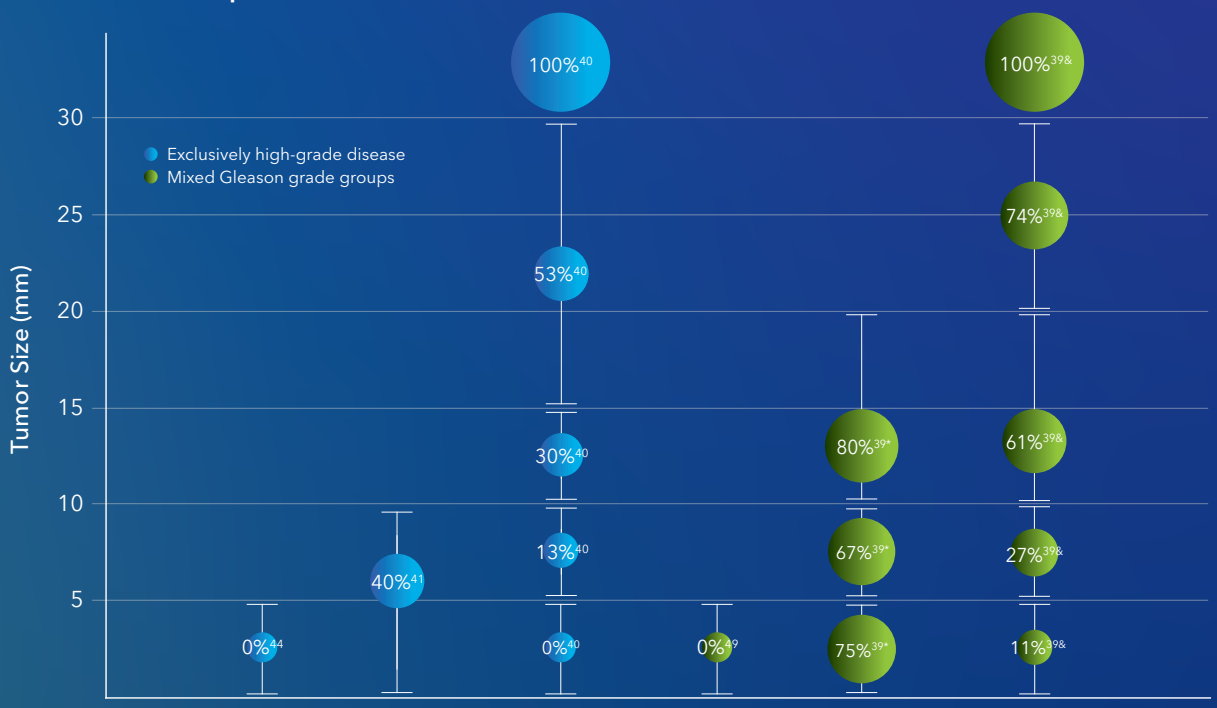


Figure 2 The impact of tumor size on mpMRI tumor detection. Bubble size reflects the percentage (%) of tumors detected by mpMRI: larger bubbles indicate a higher detection rate than smaller bubbles.

- *Sizes based on solitary tumors
- &Sizes based on multifocal tumors
- Green bubbles are mixed Gleason grade groups while blue bubbles are exclusively high-grade disease (≥GG2) [39-41, 44, 49]

3. Tumor Size

Tumor size is a critical factor for mpMRI detection. Studies employing whole-mount radical prostatectomy demonstrate the relationship between tumor size, multifocality, and tumor detection.[5,39,40,41] Although tumors greater than 1 cm can be missed by mpMRI, tumor detection decreases as tumor size decreases.[39-42,44] Also, small tumors are understood to harbor high-grade disease. [5,42,44]

4. Invisible Tumors

Up to 55% of all prostate cancer and 35% of HGPCA tumors are not visible on mpMRI.[5,28,43] In addition to size, grade, and multifocality, specific tissue architecture (cribriform) reduces tumor visibility.[49] Moreover, gene expression appears to be involved with poor cellular organization in tumor visibility, at least to some degree. Interestingly, visible and invisible tumors have similar outcomes: biochemical recurrence, distant metastasis, and prostate cancer-specific mortality and do not impact genomic test scores.[50,47]

5. PIRADS Variation

PIRAD scores are risk assessment categories that share the limitations of all risk assessment tools regardless of type - biomarker, nomogram, or tissue-based test.

A PIRADS category provides a probability – not a guarantee – of the result to be found at biopsy. Studies that have biopsied all PIRADS results have displayed the diverse range of HGPCA in each category, low-risk cancer (GG1), and benign tissue that makes up varying degrees of each PIRADS category.[3, 34, 57, 74, 76]

6. False Positives

Many factors impact appropriate MRI-specific tumor detection. Conditions such as hyperplasia, inflammation, fibrosis, prostatitis, and high-grade prostatic intraepithelial neoplasia (HGPIN) can cause false positive MRI readings.[36]

7. False Negatives

Tumor size, multifocality and tissue architecture can all contribute to false negatives. But, tumor location is also important to mpMRI detection. Studies find lesions in all zones - peripheral, transition, and anterior regions.[13,25,28,37,38] Serrao *et al*, demonstrated that 50% of mpMRI false negatives were located in the anterior region. In contrast, Kido *et al*, utilized radical prostatectomy to note that 53% and 47% of MRI undetected tumors were in the peripheral and transition zones, respectively.[37,38]

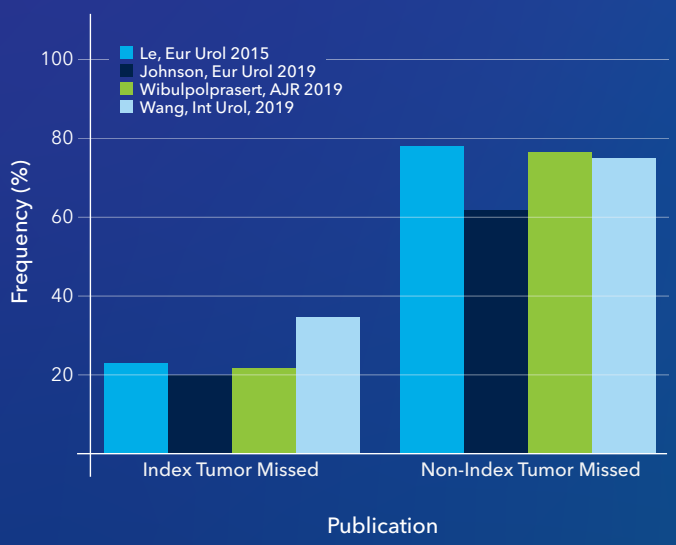


Figure 3 Studies investigated mpMRI ability to detect multifocal disease. Although mpMRI misses the index lesion 20%-30% of the time, non-index lesions are missed much more frequently (63%-79%).

mpMRI Performance

Comparing mpMRI performance across studies is difficult because of study variation, which includes everything from different equipment (e.g., magnet strength) to consistent incorporation of the three (3) individual phases (T2 weighted, diffusion, and DCE), as well as reader experience. Study design is as guilty, if not more so, than equipment standardization for much of the difficulty in assessing and comparing MRI metrics. Biopsy methodology varies greatly, as does which samples are evaluated; studies often mix biopsy naive cases with prior negative biopsies and/or samples from men on active surveillance.[25, 53-55] These 'mixed use' inclusion criteria impact disease prevalence which affects positive and negative predictive values.[53]

Even the definition of HGPCA is not consistent across mpMRI studies. While many use ISUP grade group 2 or higher (≥GG2), other definitions also include core length or percentage of cores positive, or ISUP grade ≥GG3.[20, 56-61] Mortezavi *et al*, illustrates how HGPCA definitions and biopsy methodology impact HGPCA incidence.[62]

mpMRI Negative Predictive Value (NPV)

As mentioned, mpMRI seems better at finding larger, higher-grade solitary tumors than multifocal tumors.[5,39-41,60] Positive predictive values (PPVs), or the likelihood that the positive MRI will find HGPCA, vary but trend upward as PIRAD scores increase.[23,51,58]

When it comes to negative or low-risk MRI results (PIRADS<3), the range of negative predictive values (NPV) is wide.[20,25,43,51,53-62] Some data suggests 'good' mpMRI NPV on a per patient basis but not on a per lesion basis.[57] Arguably, NPV is more concerning than PPV because negative mpMRI results are used to avoid biopsy,[28] and concerning HGPCA (≥GG2) is often found after a negative or low-risk mpMRI.[21,51,56] Chung *et al*, examined 'invisible' tumors (PIRADS <3) with both biopsy and radical prostatectomy (RP). They found that, at biopsy, 24% and 6.6% were ≥GG2 and ≥GG4 respectively.[63] One study even found that 17% of men with 'normal' mpMRI readings had palpable disease.[51] Kinnaird *et al* examined men initially classified as mpMRI negative at 2-4 years post-imaging and found that the false negative rate was 23% for HGPCA.[64] Guidelines reflect published data emphasizing that, by itself, a negative mpMRI does not omit the possibility of cancer and clinicians should consider biomarkers when looking to defer a biopsy in a patient with a negative mpMRI.[3]

Early studies presented NPV claims based on small numbers of cases, muddled mixed biopsy sample types (biopsy naive, prior negative, active surveillance) without sub-analysis, varied disease prevalence, or a combination that impacted NPV.[15,65] Moldovan *et al* did a thorough review of studies documenting how clinical heterogeneity and disease prevalence impacted NPV results for HGPCA that ranged from 64% to 88%. Therefore, we only included studies that were either published after the Moldovan *et al* review or were not cited in their study.[65]

Studies continue to mix and match different biopsy sample types resulting in different disease prevalence that impacts PPV and NPV.[25,53-55,61] Several also use alternate definitions of HGPCA that include core number or percent of core positive.[20,56,60] Fortunately, some studies conduct sub-analysis to examine metrics separately based on biopsy type[54,56,62,66] (FIGURE 4).

Studies that utilize a more holistic assessment of the prostate, employing template biopsy mapping, saturation biopsy, or whole mount radical prostatectomy, offer the most comprehensive pathologic ground truth for assessing performance metrics.[5,56,57,60,67] One of the most comprehensive studies to provide a detailed assessment of mpMRI metrics was the PROMIS study.[56] The PROMIS study did many things well; high-quality and standardized MRI, in depth reporting, dedicated and experienced urologic radiologists, centralized reader training, as well as high-quality targeted biopsies. PROMIS researchers performed template mapping biopsy every 5 mm and a TRUS biopsy on every man: an approach that provides a much better understanding of the prostate than TRUS or fusion biopsy. One potential criticism of the PROMIS study was the use of 1.5 Tesla magnets instead of the 3 Tesla magnets most currently use. However, much of the essential mpMRI

literature has utilized a mix of magnet strengths, including PRECISION, MRI-FIRST, STHLM3-MRI (NCT03377881).[22,23,33] Furthermore, some researchers have found no difference in PPV or NPV when comparing 1.5T or 3T generated data.[6,20]

The PROMIS study had three definitions of clinically significant cancer: (1) ≥GG3 or cancer core length ≥6 mm, (2) ≥GG2 or cancer core length ≥4 mm, and (3) ≥GG2. Each include different performance metrics. The primary definition (≥GG3 or cancer core length ≥6 mm) resulted in a PPV of 51% and NPV of 89%. But ≥GG2 is widely utilized as the definition of HGPCA in clinical practice, and PROMIS observed that for ≥GG2, the PPV was 65% and NPV was 76%.

Other studies have utilized mapping biopsies and demonstrated similar NPVs for ≥GG2 or related definitions. Simmons *et al* noted an NPV of 68.6% for ≥GG2 and/or tumor length of ≥4 mm.[60] Mortezavi *et al* used template saturation biopsy to measure mpMRI performance metrics for ≥GG2 and noted overall NPVs of 74.2% and 68.5% for saturation biopsy and targeted fusion biopsy, respectively. They also did subgroup analysis by prostate sample type (naïve or prior negative biopsy) resulting in NPVs that were changed due to the impact of disease prevalence on NPV and PPV.[62] In a retrospective analysis, Hogan recently observed an NPV of 95% for HGPCA and took a higher number of cores (median=26), but they did not utilize saturation biopsy. They hypothesize their improved measurements are because they employed one highly experienced, centralized reader.[59]

mpMRI Cost

mpMRI is used widely in the United Kingdom, but mpMRI usage varies significantly from country to country in Europe; surveys show that cost is the main reason mpMRI is often not employed.[68] mpMRI is an expensive procedure with a median cost of $4396 (IQR $2,784-$7,127) for MRI-guided biopsy with imaging contributing significantly (median of $1,704) to that total. If anesthesia is utilized, the total cost increases to $5,832.[69]

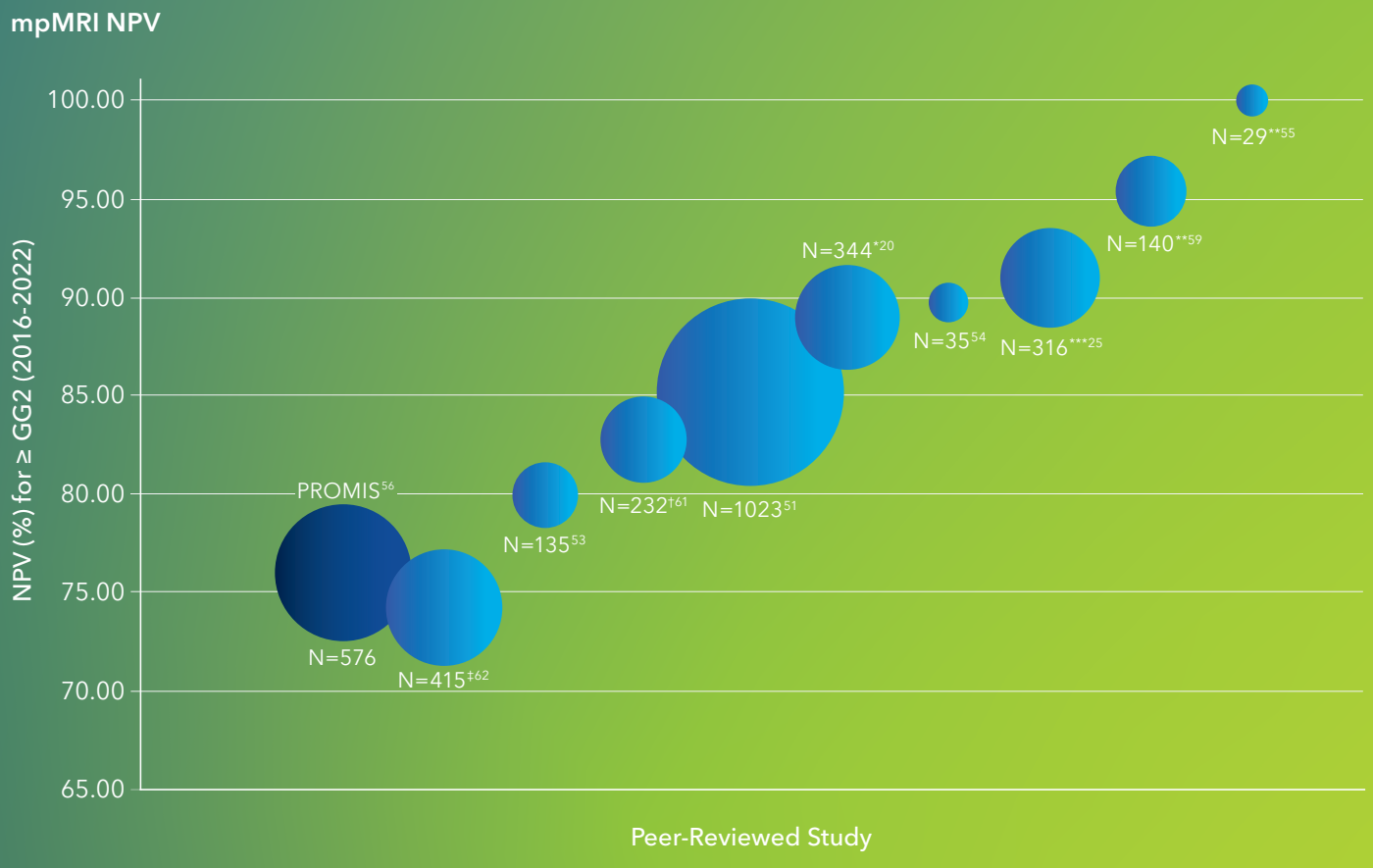


Figure 4 References reviewed in Moldavan *et al*.[64] are excluded except for the PROMIS study.[56] All NPVs reported for HGPCA are defined as ≥GG2 unless a specific notation is included. Ball location on the Y axis indicates NPV while ball size indicates cohort size.

*NPV for ≥GG2 with ≥10% of cores positive or ≥5mm in any core.
**One (1) skilled reader
***55% of cohort with initial biopsy, 30% with prior negative biopsy and 16% on active surveillance.
†81% of cohort with initial biopsy, 19% with prior negative biopsy.
‡39% of cohort with initial biopsy, 61% with prior negative biopsy.

ExoDx™ Prostate Test

Exosomes are very small (30–150 nanometers (nm)) vesicles containing DNA, RNA, and proteins and are produced and secreted in large quantities from every cell in the body. In healthy individuals, billions of exosomes exist per milliliter (mL) of plasma.[70,71] In addition to blood, exosomes are found in all bodily fluids (urine, cerebrospinal, breast milk, saliva, etc.). Exosome signaling has a critical advantage over classical, soluble signaling pathways as exosome signaling does not decrease over distance. Integral to the development and propagation of multiple diseases, exosomes are involved in normal physiology and cancer alike.[72,73]

The ExoDx Prostate Test is a non-invasive urine assay that does not require a digital rectal exam (DRE) and analyzes three exosome-located genomic markers that are associated with high-grade prostate cancer (HGPCA) defined as ≥GG2. The ExoDx Prostate Test is validated for use in men with initial or repeat biopsy (NCT02702856 and NCT03031418) who are 50 years or older and have PSAs between 2–10ng/mL.[74,75] ExoDx Prostate is a continuous risk assessment tool that results in a risk score: the risk of high-grade prostate cancer (≥GG2) increases as the score increases.

ExoDx Prostate Test helps make more informed decisions on which patients may likely benefit – or not – from a prostate biopsy. In a randomized controlled two-arm trial (level 1 evidence) – one arm used standard of care (control arm) to guide patient management. In contrast, in the other arm, clinicians received and integrated the ExoDx Prostate Test results into their shared decision-making with patients. This study demonstrated that the ExoDx Prostate Test was able to defer biopsy in men unlikely to find HGPCA, suggest which men were at higher risk and should have a biopsy, and consequently detect 30% more HGPCA in the ExoDx Prostate Test arm than in the standard of care arm.[76]

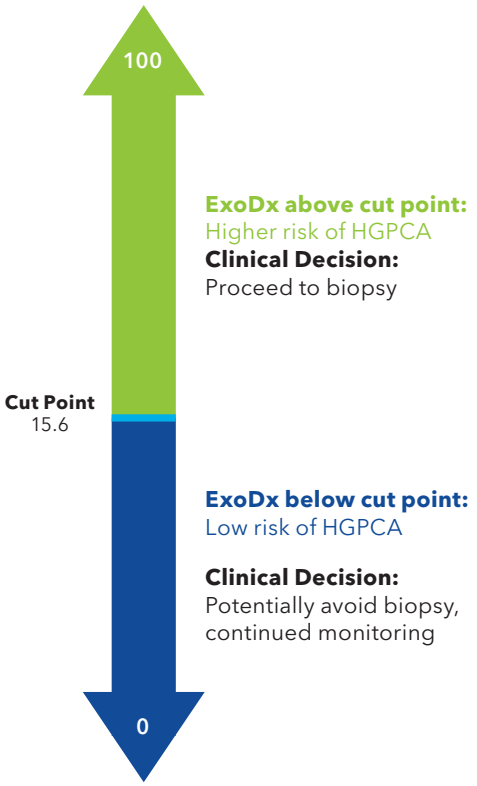
The ExoDx Prostate Test Performance

Genomic assessment using the ExoDx Prostate Test is significant compared to any individual clinical feature or combination of features. In validation studies, the ExoDx Prostate Test was compared to an optimized standard of care model (not found in clinical practice), clinical risk calculators such as PCPT and ERSPC, as well as clinical features (PSA), and was significantly more accurate than either optimized standard of care clinical models, risk calculators or PSA. Adding the standard of care information to the ExoDx Prostate genomics did not improve test performance – the genomic information was significantly more accurate as measured by the area under the curve (AUC).

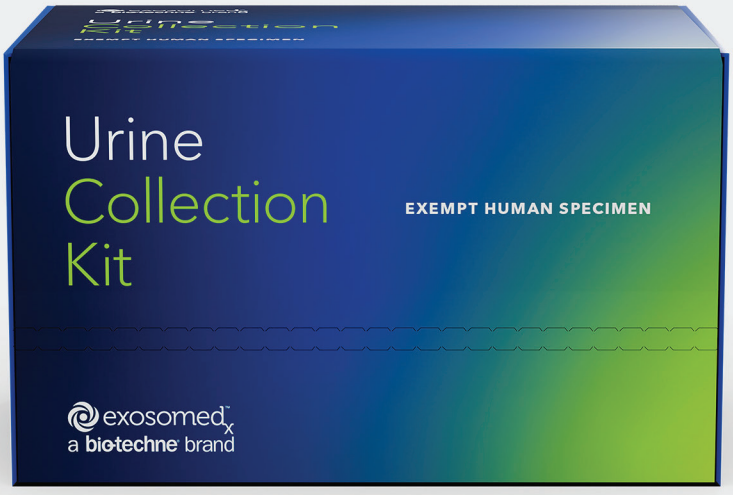
The ExoDx Prostate Test has validated high NPVs of 91.3% for ≥GG2 and 97% for ≥GG3, while the PROMIS study demonstrated 76% NPV for ≥GG2. It's important to note that the ExoDx Prostate Test, like most tests, was validated on biopsy which is the 'gold standard.' The PROMIS NPV was based on a template mapping biopsy which is more complete. However, the ExoDx Prostate Test was assessed in some patients that subsequently had RP, and we found that the ExoDx Prostate Test PPV improved while its NPV stayed the same.[76] These results must be investigated on a larger scale. Until a direct head-to-head comparison of mpMRI and the ExoDx Prostate Test in the same cohort is conducted, we will not know the comparative performance metrics. Until that study is performed, we will look at the best data available: the ExoDx Prostate Test validation studies and the PROMIS trial.

Logistics and Convenience

In comparison to mpMRI, the ExoDx Prostate Test is straightforward to use. The ExoDx Prostate Test only requires a urine sample and does not require a digital rectal exam (DRE). In fact, due to the ExoDx Prostate Test's ease of use, a home sample collection kit was developed and deployed early during the COVID-19 pandemic. The home collection kit will continue to be a boon to clinicians and patients as prostate biopsy is forecast to be the outpatient procedure most often to burden urologists.



ExoDx™ Prostate Test



MRI and ExoDx™ Prostate

Combining risk assessment methods - such as mpMRI and biomarkers – (when appropriately applied) can better inform clinical decision-making. Published data demonstrates that combining different types of biomarkers, be it PSA density, risk calculators, or genomic testing, can provide enhanced assessment when appropriately layered with mpMRI in a clinical pathway.[53, 58, 61, 67]

Until mpMRI and biomarkers are incorporated into well-designed RCTs, we will not truly understand the most beneficial way to integrate the two technologies. Nevertheless, based on published information, we can hypothesize how biomarkers, specifically the ExoDx Prostate Test, may be combined with mpMRI to answer the question. de la Calle *et al* performed an observational analysis of men who had both mpMRI and several different biomarkers including the ExoDx Prostate Test. This work, independent of Exosome Diagnostics involvment or sponsorship, was originally published in an abstract form and eventually as a published article.[7,79]

The authors developed a series of algorithms that provide perspective on the possible results of combining the ExoDx Prostate Test and mpMRI in various clinical paths.[7] Recreated (FIGURE 5) de la Calle *et al* highlights that the ExoDx Prostate Test use alone might avoid a significant percentage of biopsies while only deferring <5% of HGPCA detection. Moreover, employing the ExoDx Prostate Test and mpMRI together (algorithm #4) avoids both likely unneeded mpMRIs and biopsies without delaying the detection of any additional HGPCA.[7]

Preliminary work at Exosome Diagnostics investigating the ExoDx Prostate Test and mpMRI showed an association between rising ExoDx Prostate Test scores and PIRAD scores, (FIGURE 6). Our research also demonstrates the potential benefits of modeling the ExoDx Prostate Test and mpMRI together (FIGURE 7). Based on a retrospective analysis of 93 men aged ≥50 years with PSA 2-10 ng/ml under consideration for a prostate biopsy that received an MRI, an ExoDx Prostate Test, and a subsequent biopsy we determined that the ExoDx Prostate Test and MRI provide independent sources of information and in combination perform better than individually.

Possible Integration of ExoDx Prostate Test, mpMRI, and PSAD

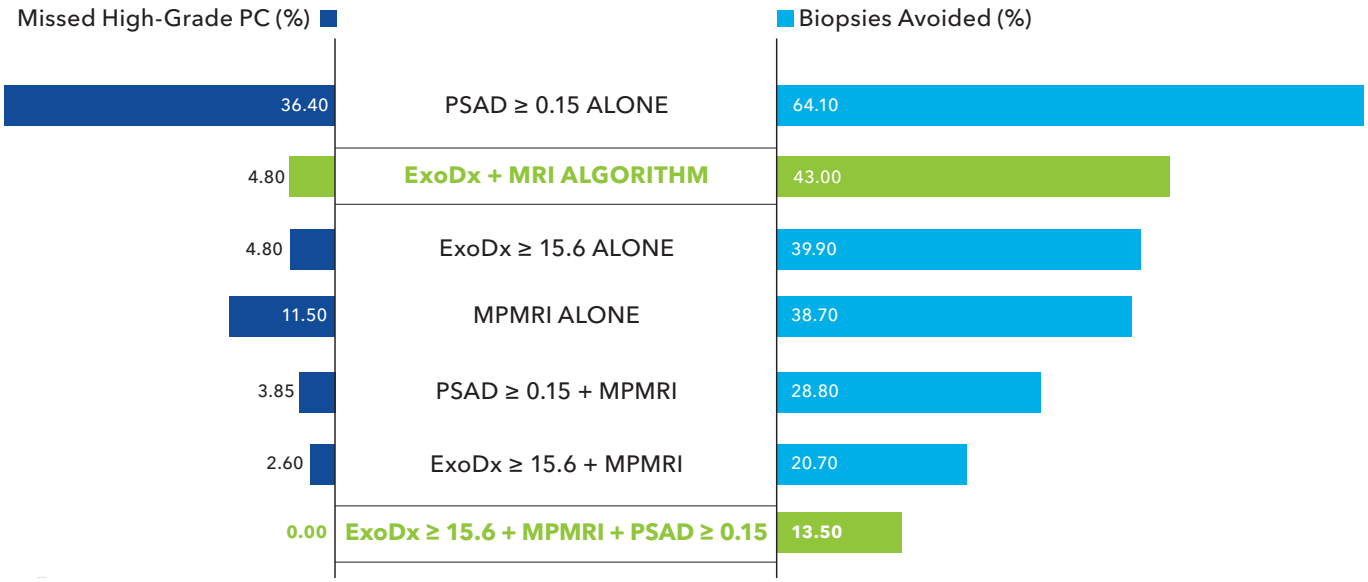


Figure 5 Figure recreated from de la Calle *et al* 2020. In this study, independent of Exosome Diagnostics involvement or sponsorship, synergy between the ExoDx Prostate Test and mpMRI was shown by de la Calle *et al*. The study compared PSAD alone, ExoDx alone, mpMRI alone, PSAD + mpMRI, ExoDx + mpMRI + PSAD and an ExoDx + MRI algorithm (defer mpMRI and Bx below the ExoDx cutpoint (15.6), but have mpMRI if the ExoDx result is between 15.9 and 19 but Bx only if the MRI is positive. If ExoDx>19, obtain MRI and Bx regardless of MRI results). Elevated PSA was considered <20ng/mL.

ExoDx Prostate Test and mpMRI Association

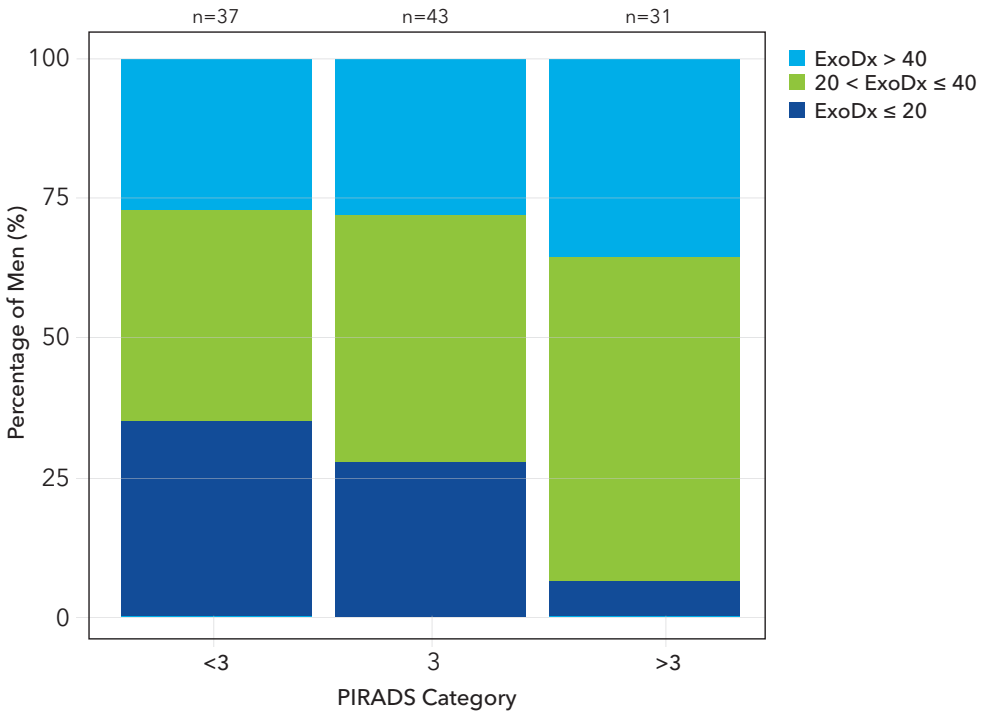


Figure 6 Do ExoDx and MRI provide independent or the same (correlated) information? ExoDx and MRI are neither perfectly correlated nor orthogonal. Preliminary data indicates that the prevalence of both higher Gleason grade groups and higher ExoDx Scores increase with higher PIRADS Scores indicating a degree of correlation.

Modeling Potential ExoDx Prostate Test/mpMRI Combination

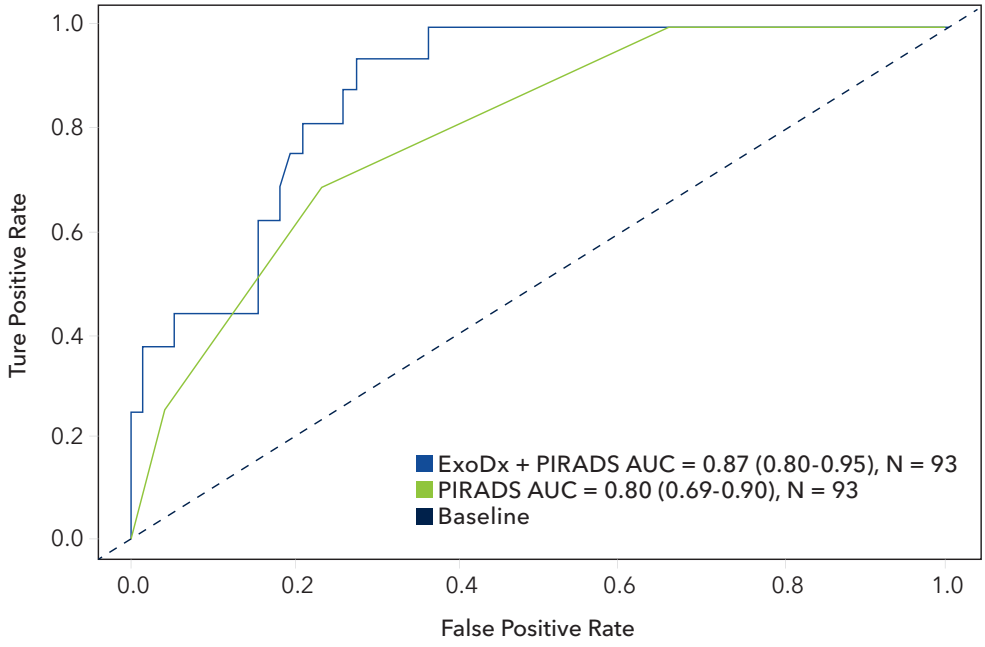


Figure 7 Preliminary modeling of combining ExoDx and mpMRI suggests superior area under the curve (AUC), with AUCs of 0.87 and 0.80 for the PIRADS +ExoDx model or PIRADS alone respectively. By DeLong's test, PIRADS+ExoDx performs better than MRI (p=0.023). This data supports the complementary value of a combined biomarker/mpMRI model.

Conclusions

All risk assessment methods, including mpMRI or biomarkers, have strengths and limitations. The key to more informed clinical decision-making is to really understand each technology's limitations and consider the appropriate integration of complementary risk assessment methods. There is a vital need to understand better how mpMRI and various biomarkers can provide more value to clinical practice; indeed, the newly formed ReIMAGINE Consortium was explicitly born to develop risk assessment tools that can examine the benefits of combining mpMRI with biomarkers.[8]

Biomarkers, in particular the ExoDx Prostate Test, have a complementary role with mpMRI. Combining the ExoDx Prostate Test with mpMRI has potential benefits for maximizing detection of HGPCA while minimizing HGPCA that may be missed by either method alone.

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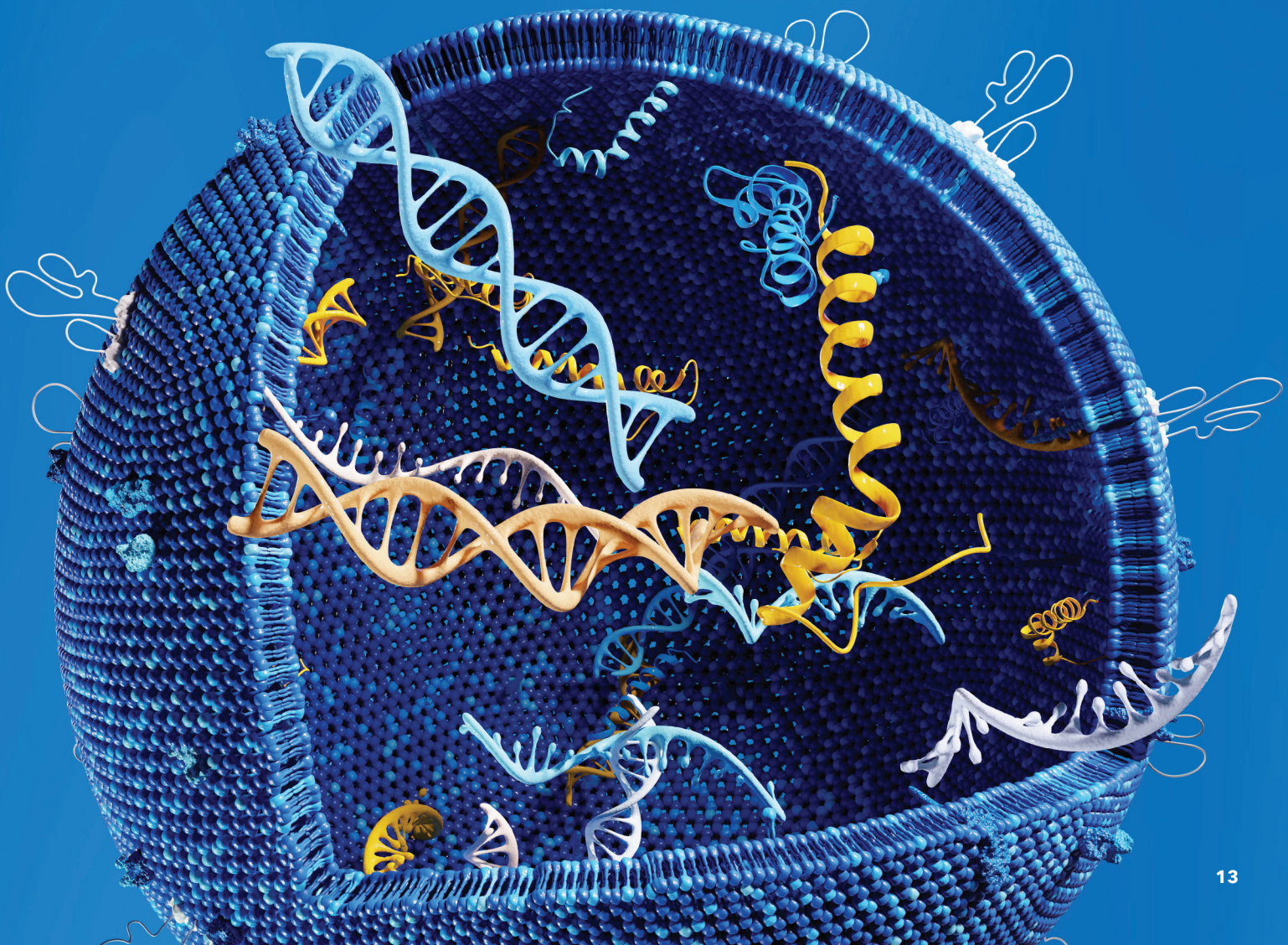

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