Haystack MRD™: A unique approach to tumor-informed minimal residual disease testing

Why the highly specific Haystack Duo™ technology is necessary for ultrahigh sensitivity

Introduction

Haystack MRD is a circulating tumor DNA (ctDNA)-based test that profiles a patient's tumor and tracks ground-truth somatic mutations in blood to inform minimal residual disease (MRD) status.

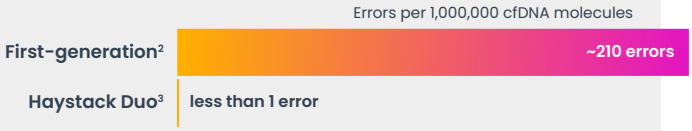
It is well accepted that tumor-informed, personalized MRD is significantly more sensitive than tumor-naive approaches.[1] However, various methods are used for tumor-informed MRD, and it is difficult to know which test to choose. One significant difference is the wide range of mutations that are tracked, from 16 to more than 1,800. Understanding how the number of tracked mutations relates to test performance is key to selecting the most robust MRD test to help inform clinical decisions and to support therapeutic development.

Haystack MRD increases sensitivity without sacrificing specificity

Every mutation tracked provides an additional chance to detect ctDNA molecules in a patient sample. However, traditional MRD tests generate background noise proportionate to the number of mutations that are tracked. Most next-generation sequencing (NGS) methods used for MRD testing are not specifically designed to reduce this noise, so tracking a greater number of mutations with these tests yields diminished returns, as the theoretical improvement in sensitivity is obscured by the increased number of technical errors that inevitably arise from the laboratory workflow.

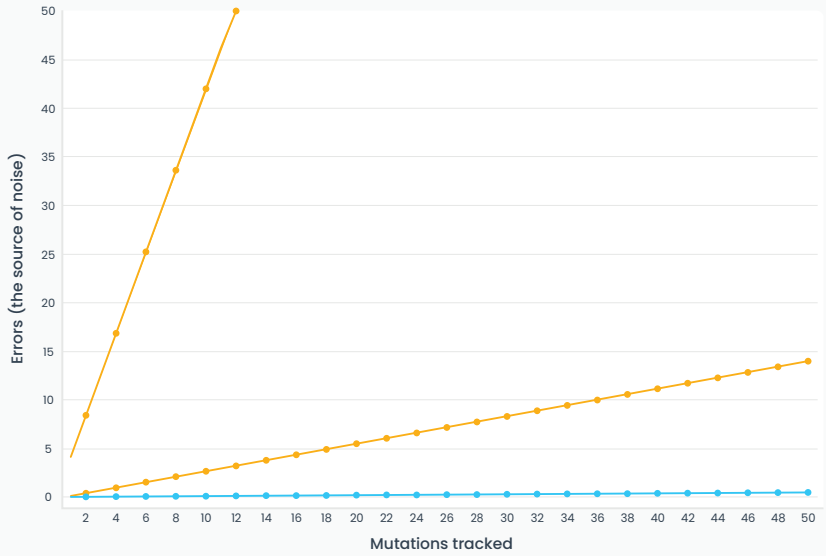
As an example, the NGS method used by a first-generation personalized MRD test yields about 210 errors for every 1,000,000 cell-free DNA (cfDNA) molecules sequenced.[2] In contrast, Haystack Duo™, the chemistry behind Haystack MRD, yields fewer than 1 error for every 1,000,000 molecules sequenced[3]—an error rate more than 200 times lower than that of first-generation technology.

Haystack Duo reduces error rate to 200x lower than first-generation MRD technology



This extremely low error rate provides two advantages:

- Haystack MRD can call the lowest levels of MRD with confidence, without increased risk of false positives.[3] In other words, the test achieves superior sensitivity while maintaining high specificity. **The result is greater confidence in discerning which patients may benefit from additional treatment versus those who can likely avoid the side effects and cost of unnecessary therapy.**



Rate of noise increase versus mutations tracked[3]

As more mutations are tracked, background noise increases faster for competing tests than for Haystack MRD. As a result, Haystack can call MRD at the lowest levels of ctDNA without risk of false positives.

Competitors A and B
Elevated noise obscures low-level MRD, reducing sensitivity

Haystack MRD
Minimal noise reveals ctDNA present at the lowest levels, yielding exquisite sensitivity for MRD detection

*Graph models cfDNA input of 20,000 genomic equivalents (66 ng) for all tests

First-generation MRD test providers claim that there is no benefit to increasing the number of mutations tracked beyond 16. However, this is not true for Haystack MRD.[3] Haystack Duo technology was specifically designed to keep background noise low so that a greater number of mutations can be tracked for each patient, increasing the likelihood of detecting residual or recurrent disease.

Additional benefits of Haystack MRD's ultrahigh specificity

Sufficient information for personalization from whole-exome sequencing (WES) or even from targeted sequencing

Not all cancers exhibit a large number of somatic mutations. Tests that attempt to increase sensitivity by either tracking up to 1,800 mutations or detecting rare phased variants (multiple mutations on a single DNA molecule) require whole-genome sequencing (WGS) of the tumor to reveal a sufficient number of alterations. Haystack MRD keeps noise to a minimum and, therefore, can achieve unparalleled sensitivity by tracking an optimal number of mutations identified by WES and targeted sequencing.

Higher cfDNA input increases detectability

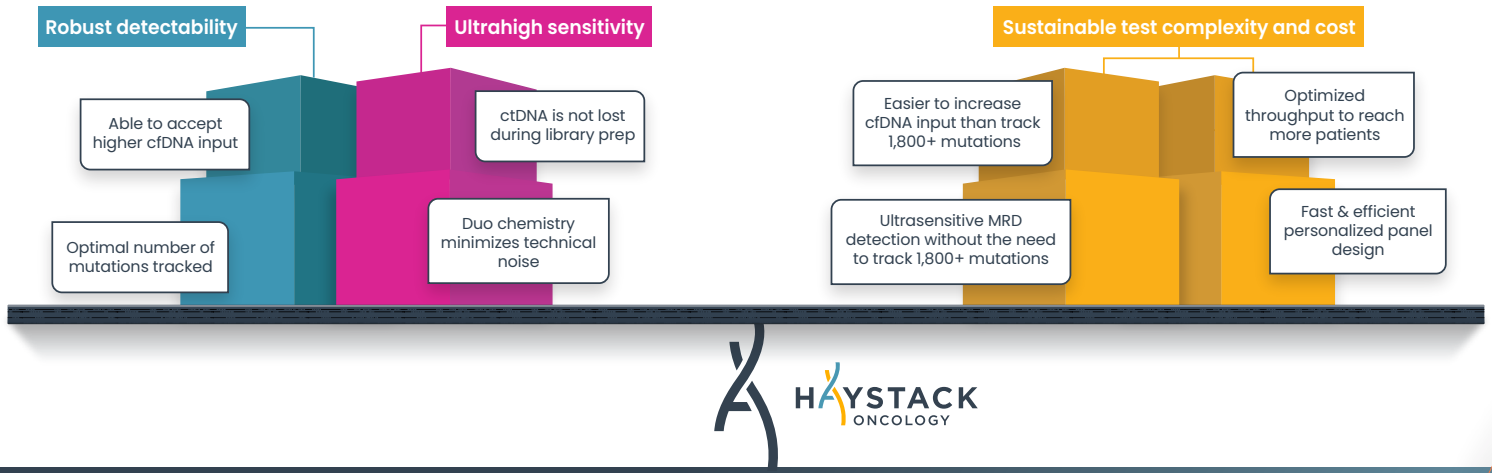
Increasing the quantity of cfDNA input into the test can also increase MRD detection, but only if noise is minimized. Other MRD tests are limited to 1–2 blood tubes because input of more material would hinder test performance due to elevated noise. Haystack MRD can accept up to 3 blood tubes, allowing for more copies of the human genome to be sequenced. Increased input yields the greatest ability to detect MRD-positive patients, even at the lowest levels of residual disease.

Confidence in MRD-negative results

Haystack MRD produces virtually zero technical noise,[3] meaning that even a very low signal indicates that MRD is present. Therefore, when Haystack MRD observes no signal, it is more likely that the patient is truly MRD-negative than with other MRD tests that exhibit elevated noise. Haystack MRD delivers better information to help decide when therapy is needed—and when it is not.

The balancing act of tumor-informed MRD

Haystack MRD achieves unparalleled performance without burdensome complexity



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To learn more about why Haystack MRD is the best source of MRD information for patients, contact us today at haystackoncology.com/contact

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1. Chidharla A, Rapoport E, Agarwal K, Linares B, Chakrabarti S, Kasi A. Circulating tumor DNA (ctDNA) as a minimal residual disease (MRD) assessment and recurrence risk in patients undergoing curative intent resection with or without adjuvant chemotherapy in colorectal cancer: A systematic review and meta-analysis. *J Clin Oncol.* 2022;40(16_suppl):3623-3623. doi:10.1200/jco.2022.40.16_suppl.3623
2. Kinde I, Wu J, Papadopoulos N, Kinzler KW, Vogelstein B. Detection and quantification of rare mutations with massively parallel sequencing. *Proc Natl Acad Sci U S A.* 2011;108(23):9530-9535. doi:10.1073/pnas.1105422108
3. Data on File. Haystack Oncology, 2023