ONCOLOGY WHITE PAPER

# Barriers to Precision Medicine:

## From Quantity Not Sufficient to Quality Care

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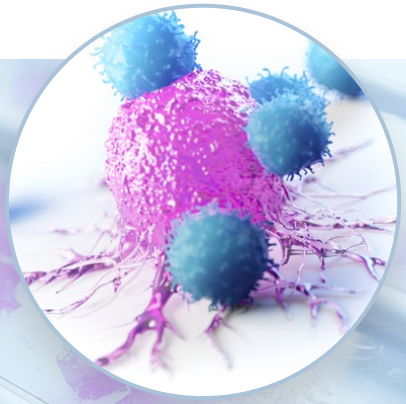
The evolution of precision medicine often provides patients with a choice of treatment options: chemotherapy or targeted therapy. While chemotherapy indiscriminately attacks rapidly dividing cells, leading to significant side effects, targeted therapy offers a more refined approach with the potential for fewer side effects and increased overall survival rates.



*While chemotherapy indiscriminately attacks rapidly dividing cells, leading to significant side effects, **targeted therapy** offers a more refined approach with the potential for fewer side effects and increased overall survival rates.*

The success of targeted therapy, however, depends heavily on precise molecular profiling, which faces substantial challenges due to the quantity and quality of tumor samples. These challenges can result in a large number of patients having to forego tumor profiling-based treatments because their tissue sample was deemed of too poor quality and quantity to warrant an NGS test or did not yield a usable result when tested. This limitation affects upwards of 25% of all samples, hindering the accurate identification of eligible patients for targeted therapy. There is a need for more sensitive molecular methods outside the NGS paradigm, particularly for samples of too low quality or quantity. Such **alternative methods could significantly expand patient access to targeted treatments, improve outcomes,** and provide a more efficient **pathway for personalized cancer care**. Integrating these novel diagnostic techniques represents a crucial advancement in oncology, bridging the gap between current molecular testing challenges and the effective administration of tailored cancer therapies.



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## Quantity & Quality of Tumor Sample Affects Treatment Options

Chemotherapy and targeted therapy are both effective methods for cancer treatment. However, chemotherapy kills fast-growing cancer cells in the body and attacks healthy cells that grow and divide quickly. As a result, chemotherapy can cause several side effects for the patient.[1] Novel treatment options that target tumors with specific molecular perturbations have been developed over the past few decades to overcome this. These targeted therapies attack cancer cells by interfering with specific proteins that help tumors grow, limiting damage to healthy cells and resulting in fewer and less severe side effects than chemotherapy.

**Targeted therapy is key for improving overall survival.**

Moreover, targeted therapy is key for improving overall survival. Patients identified for and placed on targeted therapy regimes have shown dramatically improved overall survival (OS) and progression-free survival (PFS) compared to those without matched therapies.[2] Ideally, as many patients as possible should have access to targeted therapy. However, determination of eligibility for **targeted therapy depends on obtaining the tumor's molecular profile by running a molecular test.** As outlined below, the success of these molecular tests heavily depends on the quantity and quality of the tumor sample obtained, which may be problematic in many cases.

The specific method of tumor sample collection for diagnostic purposes can vary depending on the type of tumor, its location, and the purpose of the procedure. Some standard methods for collecting tumor specimens include needle biopsy, core biopsy, surgical excision, endoscopic biopsy, and fine needle aspiration (FNA). After collection, the tumor specimen

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is sent to a pathology laboratory, where it undergoes various analyses, such as histological examination, genetic analysis, and molecular testing. When tumor molecular profile analysis is performed, it is most often conducted by next-generation sequencing technology (NGS).

## Varying Tumor Sample Collection Methods, Varying Results

Depending on the type of tumor, availability of material, and the downstream application, tumor material available for molecular testing may be in various forms, but the most common is formalin-fixed paraffin-embedded (FFPE) samples. DNA extracted from FFPE samples can vary widely in quality due to age, fixation conditions, DNA-protein crosslinking, and the presence of inhibitors, which may impact downstream genomic analyses. Furthermore, FFPE-derived DNA is typically degraded into small fragments, with peak fragment sizes as low as ~180 base pairs (bp).[3] Therefore, even with recent advances in DNA extraction and NGS-library preparation protocols, it is necessary to thoroughly assess DNA quality and quantity prior to molecular analyses.[4]

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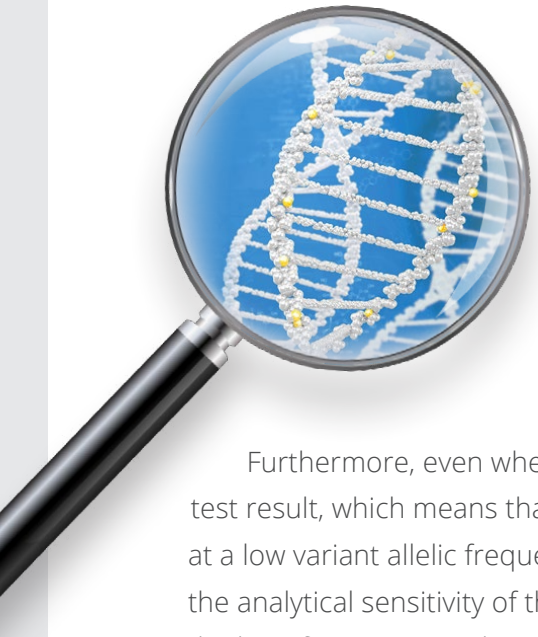
In addition to requiring a certain level of DNA quality and quantity, NGS-based molecular profiling requires a minimum fraction of tumor cellularity. This varies from lab to lab and depends on the actual sequencing approach used – i.e., targeted panels vs. whole exome sequencing (WES) or whole genome sequencing (WGS) – but generally, a minimum of 20% tumor cellularity is necessary. **For many tumor specimens, these quality, quantity, and tumor content criteria cannot be met; hence, a significant fraction of samples cannot be tested. These samples are usually referred to as QNS (quantity/quality not sufficient).**



## When Tumor Samples are Classified as QNS

It is important to note that even when samples meet the criteria and are evaluated through a Next-Generation Sequencing (NGS) based molecular test, there is a chance that the test may not return any result. This could be due to various factors that may negatively affect the NGS library preparation, such as a lower-than-expected tumor fraction, insufficient quantity of nucleic acids, high level of degradation, or contamination of the extracted sample with inhibitors.

Furthermore, even when the NGS analysis is successful, it is possible to get a false-negative test result, which means that no somatic variant was reported despite it being present in the tumor at a low variant allelic frequency (VAF). This could occur when the frequency of the variant is below the analytical sensitivity of the sequencing approach, caused by insufficient sequencing depth or the bioinformatics pipeline that was used.

The fraction of samples submitted for NGS-based molecular testing that are classified as QNS, do not return a result, or return a false-negative, can account for up to 25% of all samples.[5] Without molecular information, it is impossible to determine potential eligibility for targeted therapy in certain patients. While these patients receive standard care, they do not benefit from targeted treatment. Reducing the test failure rate would increase the likelihood of more patients receiving targeted therapy and potentially better outcomes.

## Conclusion

While chemotherapy and targeted therapy have proven effective in cancer treatment, the latter offers a more precise approach with potentially fewer side effects and improved patient outcomes. The efficacy of targeted therapy, however, hinges significantly on the accurate molecular profiling of tumors, which is currently challenged by the limitations associated with sample quality, quantity, and tumor cellularity in Next-Generation Sequencing (NGS) analysis. A substantial fraction of samples classified as QNS, failing to return results, or yielding false negatives, underlines a critical gap in molecular testing, directly impacting patient access to targeted therapies.

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**of tumor tissue samples due to insufficient tumor content for NGS.[5]**

**Alternative approaches, like the MassARRAY® System and ddPCR, are more accommodating of challenging samples** and less reliant on complex bioinformatics for interpretation. Leveraging other technologies beyond NGS could dramatically increase the number of patients receiving tumor profiling data that is informative to their treatment. This evolution in molecular diagnostics could be a pivotal step towards ensuring that more patients benefit from the advancements in targeted cancer therapies. As the field progresses, it is imperative to focus on developing and **integrating these novel diagnostic methods to bridge the gap between molecular testing challenges and the effective delivery of personalized cancer care.**

## References

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