# Actionable Intelligence on Pharmacodynamic Effects Improves Clinical Studies

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## Introduction

Research and medical professionals are beginning to understand the promise of insights derived from heterogeneity of treatment response within an individual patient. While the broader scientific community has long recognized that not all patients respond the same to a given therapy, valuable and quantitative knowledge related to intra-patient heterogeneity has remained largely hidden and unusable.

Two previous AIQ-sponsored white papers reveal how new technology is changing this dynamic and delivering actionable intelligence—meaningful information delivered at the right time to drive critical decision-making—into the hands of a growing number of healthcare stakeholders. In "AIQ Technology: A Next Generation Platform for Treatment Response"[1] (White Paper 1), authors explored how AIQ's novel technology platform is improving decision-making by helping clinicians and researchers uncover valuable information related to heterogeneity of pharmacodynamic (PD) effects for complex diseases such as metastatic cancer. In tandem, "Intra-Patient Heterogeneity of Treatment Response in Complex Diseases"[2] (White Paper 2) provides further evidence of how combining quantitative spatiotemporal heterogeneity metrics for lesions with their anatomical location can produce insights that impact clinical outcomes across multiple complex diseases.

The value proposition of these advancements and findings for clinical studies is significant. As the pharmaceutical industry continues its progression into larger, more expensive randomized Phase II studies, the risk in terms of finances, resources and time becomes much greater, especially when there is limited understanding of an asset's efficacy potential. AIQ technology enables pharmaceutical companies to evaluate novel therapies faster and with fewer patients by providing actionable intelligence to support accelerated go/no-go decisions during early-stage drug development. This novel platform, which has been used in more than 13 academic and pharma-sponsored clinical studies, offers many life science applications. Four are discussed below.

## Applications

### 1: Early quantification of PD effects in individual lesions

Without insights into intra-patient heterogeneity, clinical trials must proceed with an incomplete data set, often requiring longer observation and analysis timeframes that can significantly increase costs. This valuable information is often missing due to the impracticalities of assessing individual lesions within a single patient via manual methods of data extraction. The better alternative is automatic quantification of whole body and region-based disease burden response, possible only through AIQ technology, which enables rapid identification and quantification of the PD effects on individual lesions. One study[3], presented in White Paper 2, reveals how this quantification can enable early prediction of clinical outcomes through mid-treatment assessment of total disease burden, which is the sum of Standardized Uptake Value (SUV) for all body lesions - SUVtotal.

While conventional drug development emphasizes maximizing tumor response, results generated by AIQ's technology suggest that understanding and treating resistance is a promising alternative strategy. Findings from the same 2017 study[4], also presented in White Paper 2, concluded that targeting lesion resistance to a particular treatment will have a greater clinical impact and will prolong the clinical benefit of a particular therapy.

Notably, the ability to quantify region-based disease heterogeneity can be a better measure of outcomes than total disease burden. This was the finding of a 2019 study[5] where researchers investigated the impact of anatomic location of lesions in metastatic prostate cancer patients on predicting prognosis. They found that multivariate machine learning models, including region-specific disease burden metrics (c-index=0.727), outperformed that of whole-body disease burden metrics (c-index=0.705) in predicting progression-free survival.

Research also reveals that treatment response heterogeneity may be a predictor of benefit duration. A 2019 study[6] investigated the spatiotemporal change in tumor burden using AIQ technology in 22 patients with metastatic prostate cancer. They found that increase in intra-patient heterogeneity was associated with quicker disease progression and that heterogeneity in PD effect predicts benefit duration, as shown in Figure 1.

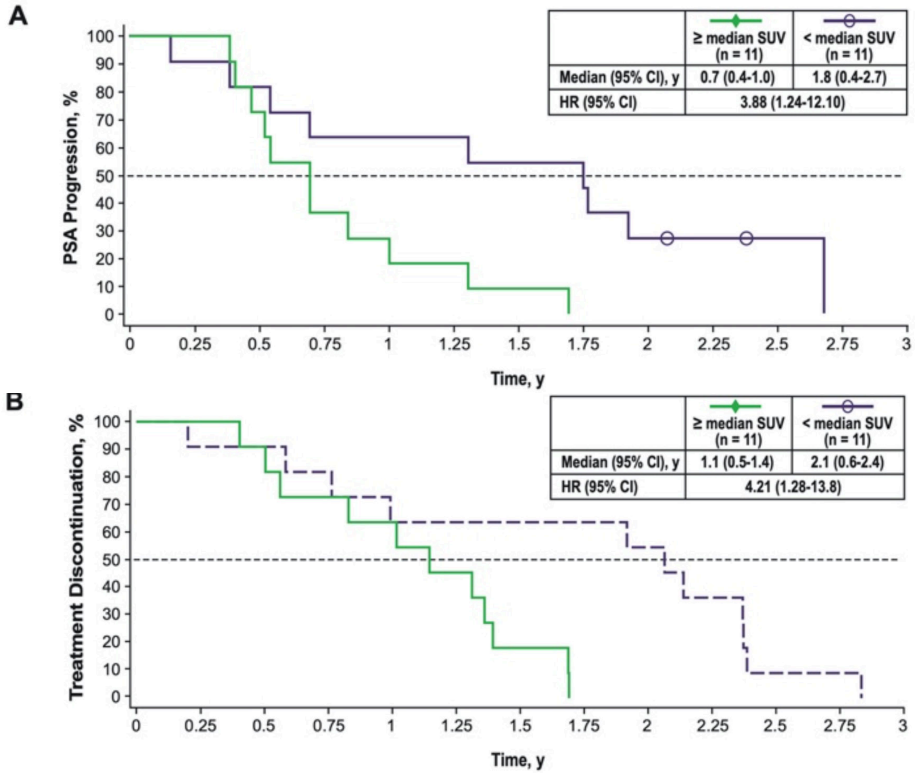


**Figure 1**. Time to (A) clinical progression and (B) treatment discontinuation by change in $SUV_{hetero}$, a standardized indicator of treatment response heterogeneity. Patients with treatment response heterogeneity greater than the median had much shorter time to clinical progression and treatment discontinuation.

## 2: Understand biological drivers for mechanism of resistances through PD effects

The previous application reveals how AIQ's technology can enable early assessment of individual lesions and region-based disease burden. It allows early prediction of clinical outcomes and demonstrates the value proposition of targeting resistant lesions and gathering data related to disease response early in a clinical trial.

Drilling deeper, quantitative measurement of an individual lesion's disease resistance can help researchers better understand the corresponding biological drivers. A study[7] presented in White Paper 1 demonstrates how use of AIQ technology can direct biopsy of non-responding lesions for better understanding of therapy resistance. The previously discussed 2019 study[8] further supports this assertion. The investigation, which included analysis by both AIQ technology and circulating tumor cell (CTC) tests, found that the expression of Enzalutamide resistance genes, AR-V7/9, and neuroendocrine expression SYP increased substantially at the time of clinical progression. This shows how analysis of intra-patient heterogeneity can be paired with biopsies to better understand mechanisms of resistance.

## 3: Determine PD effects with fewer patients

The previous two applications revealed how imaging metrics derived from AIQ technology can accurately assess PD effect for each lesion, predict outcomes earlier in clinical trials and help better understand drug resistant mechanisms. Due to superior sensitivity, AIQ's technology also enables pharmaceutical companies to determine PD effects with a smaller patient dataset—significantly reducing the costs and complexities of clinical trials.

Repeated sampling during treatment to obtain PD biomarkers from tumor tissue biopsy is currently infeasible with traditional methodology due to invasive, impractical processes. While biomarkers derived from peripheral blood biomarkers are somewhat noninvasive and can be sampled multiple times during treatment, they provide limited insights due to the inability to account for spatial information of a lesion.

Results from a 2019[9] study investigating how SUV measurements can be used as biomarkers in immunotherapy suggests that AIQ can provide these deeper insights and help researchers determine early PD effect across a small patient dataset. After treating 17 prostate cancer patients with pTVG-HP DNA vaccine and pembrolizumab over a 12-week period, researchers found that the change in FLT SUV measurements in vaccine draining lymph node

were significantly greater than changes in non-draining lymph nodes (p=0.02), suggesting a regional immune PD effect to vaccination (see Figure 2). Further, increases in tumor FLT SUV measurements were significantly predictive of shorter progression-free survival, as shown in Figure 3.

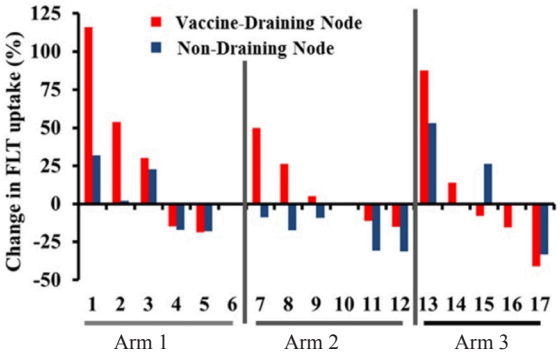


**Figure 2**. Changes in FLT $SUV_{mean}$ in vaccine draining left axillary lymph nodes are shown for each patient along with changes in non-draining right axillary lymph nodes. Patients (pts) were divided into three arms with different dosing schedules of the pTVG-HP vaccine and pembrolizumab. The difference in uptake between the draining and non-draining nodes suggests that AIQ technology can quantify a regional immune PD effect to vaccination.

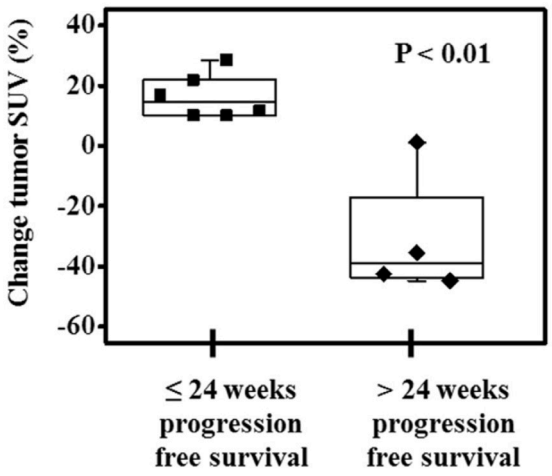


**Figure 3**. Change in $SUV_{mean}$ at 12 weeks differentiated patients with shorter and longer progression free survival (PFS). This difference was statistically significant despite the small sample size (n=17).

Another 2019[10] study investigated treatment effects of a pTVG-HP vaccine on metastatic progression in 97 patients in a randomized, double blinded, multi-institutional Phase-II trial. Use of AIQ technology across a subset of 34 patients, those with more than one scan, found that immunotherapy vaccination had detectable PD effects on micro-metastatic bone disease. SUV measurements derived from AIQ's technology were sensitive enough to detect subtle PD difference even in a dataset with fewer patients, as shown in Figure 4.

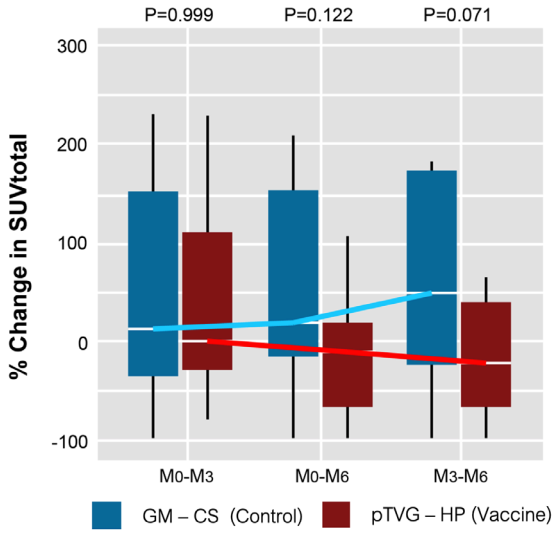


**Figure 4**. Change in $SUV_{total}$, as quantified by AIQ technology, demonstrated a decrease in disease burden of 23% for the experimental arm after six months of treatment while the corresponding control group demonstrated an increase of 53%. This difference achieved a p-value of 0.071 despite a sample of only 34 patients.

### 4: Evaluate PDs effects in novel combination or sequential therapies

The first three applications highlight how the use of AIQ technology can help assess the pharmacodynamic effect of individual lesions and response of total and region-based disease burden. They also demonstrate how this technology can be used to streamline clinical trial feasibility across fewer patients. Rapid evaluation of novel combination and sequential therapies is another significant advantage of AIQ technology. For example, a pilot study aimed at investigating a drug candidate can be used to redirect patients (e.g. with greater heterogeneity) to a different asset or combination therapy based on early quantification of PD effects. This way, clinical trials built around complex therapy options become more timely, cost-effective and efficient. Use of AIQ technology in this manner could also extend to evaluation of dosing, especially when dosing to toxicity is not ideal. A pilot study can explore different dose options by quantifying the PD effects of each.

The fourth application also addresses the need for a deeper evaluation when the clinical strategies fail. In such cases, AIQ can help investigate the failure. As research presented in this paper demonstrates, pharmaceutical companies can leverage AIQ technology to better analyze and understand the reasons for resistance or failure.

## Conclusion

The industry is just beginning to scratch the surface in terms of the opportunities to leverage actionable intelligence related to intra-patient heterogeneity in clinical trials. To that end, the flexibility of the AIQ technology platform also aligns well with the early research environment. It could be applied to research in animals and be advantageous to pre-clinical studies.

This paper demonstrates how AIQ technology can assess PD effect and disease-burden in individual lesions, as well as enable clinical trial execution across smaller patient samples. Equipped with the ability to quantify spatiotemporal heterogeneity of treatment response across all lesions within an individual patient, pharmaceutical and life science companies can now predict clinical outcomes and long-term treatment response earlier, as demonstrated by a growing body of industry evidence presented in this white paper. Moreover, AIQ technology enables rapid evaluation of a clinical strategy and guides new study designs by providing the necessary actionable intelligence to make more efficient go and no-go decisions in complex clinical trials.

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