AIQ Technology: A Next Generation Platform for Treatment Response Assessment

S. Houshmandi, PhD[i], D. Alberti, BSN, RN, MSM[ii], D. Fuhrman, MA[ii],
E. Horler, MBA, MEM[ii], S. Yip, PhD[ii]

[i]AIQ Global, Inc., San Diego, California, USA
[ii]AIQ Global, Inc., Madison, Wisconsin, USA

Introduction

It is generally accepted that not all patients respond the same to a given therapy. Less understood, however, is that not all disease sites respond to treatment in the same way even within the same patient. For complex diseases such as metastatic cancer, treatment response *within a single patient* can be highly heterogeneous.[1-5] This *intra-patient heterogeneity* of treatment response can be both spatial, or differing by anatomical location, and temporal, which is when response changes over time.

Treatment response heterogeneity is clinically relevant because resistance in a very small fraction of lesions can drive negative overall outcomes (see "Intra-Patient Heterogeneity of Treatment Response in Complex Diseases"). Traditional evaluation approaches, such as RECIST and PERCIST, focus on only 3-5 lesions; however, it is necessary to quantify treatment response for all lesions to adequately understand intra-patient heterogeneity of response and to fully identify resistance. Manual measurement of treatment response for all lesions over multiple timepoints would be complex and time-consuming, and thus clinically impractical. Some commercially available software systems can quantify overall patient treatment response, but not individual lesion response.

AIQ's technology platform quantifies spatiotemporal heterogeneity of treatment response within an individual patient, addressing all lesions. Optimized for treatment response quantification rather than diagnosis, the platform provides timely, actionable intelligence to inform treatment decisions by physicians and advance research for new therapies. Clinicians who understand intra-patient heterogeneity of treatment response can better manage the patient's disease. Similarly, pharmaceutical companies can use this intelligence to improve go/no-go decisions in early-stage drug development.

Technology Workflow

The AIQ technology platform uses radiological scans as input data. The platform is agnostic to disease type and imaging modality. The optimal scan type depends on the disease and therapy to be assessed.

Scans are first collected at baseline and then again at subsequent points in time. Delivered in standard format, those scans are uploaded to AIQ's secure, cloud-based server where AIQ's medical physicists utilize the technology platform to complete a Treatment Response Assessment (TRA). A Treatment Response Report is automatically generated, comprising quantitative treatment response metrics, spatial location, and treatment response classification for each lesion. Clinicians and researchers can easily access the results using an interactive tool or by downloading data tables. Figure 1 illustrates the technology workflow.

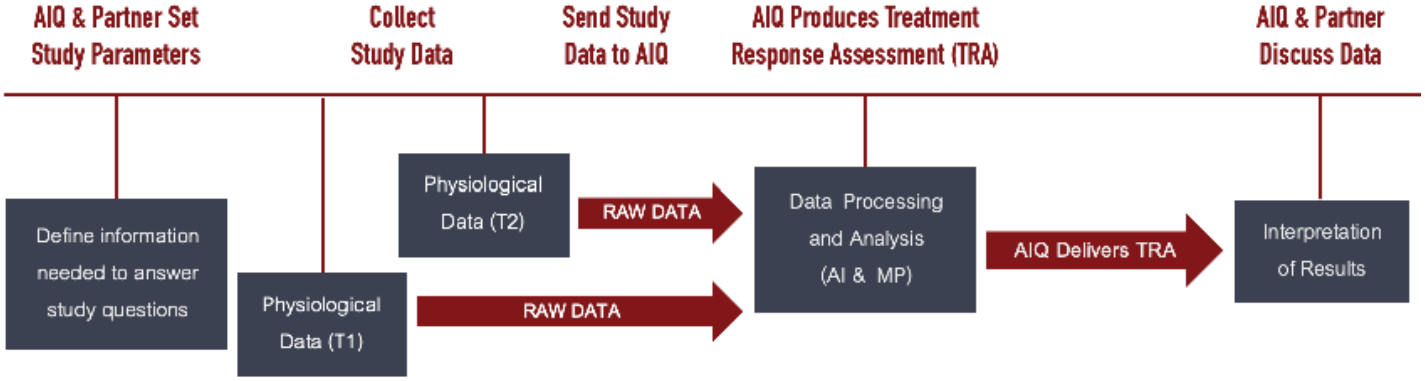


Figure 1. Schematic illustrating workflow for the Treatment Response Assessment.

Description of the Treatment Response Assessment

The TRA consists of the following steps.

A. **Data Transfer**: After scans have been uploaded, AIQ completes a quality assurance process and corrects for irregularities in the scan data. This improves the robustness of AIQ's technology in processing scans from different locations and equipment.

B. **Automatic Lesion Detection**: Individual bone lesions are automatically detected by AIQ's Statistically Optimized Regional Thresholding (SORT) method on all scans (U.S. Patent 10,445,878). First, this method segments the image into over twenty anatomical regions. Region-specific SORT lesion detection thresholds for each segment are then determined based on the analysis of over 1,750 lesions manually-identified by experienced nuclear medicine physicians. SORT thresholding achieves both specificity and sensitivity of >95% in bone lesion detection.[6]

C. **Automatic Lesion Classification**: A machine learning algorithm, random forest, is then used to classify malignant from benign lesions. AIQ's random forest algorithm was trained based on over 1,750 manually-classified lesions by experienced nuclear medicine physicians. The classification performance of AIQ's algorithm is high with both specificity and sensitivity of nearly 90%.[7]

D. **Quantitative Lesion Characterization**: Quantitative metrics are determined for each individual lesion. Specific metrics vary depending on the imaging modality, but may include volume, SUV_{max}, SUV_{total}, and SUV_{mean} (SUV refers to Standardized Uptake Value, a measurement of tracer uptake that accounts for difference in body mass).

E. **Articulated Registration**: AIQ's articulated registration algorithm (U.S. Patents 9,161,720 and 9,603,567) precisely aligns patient images from multiple scans. The technology segments the scan into skeletal regions of bones, using advanced image processing algorithms. The segmented bones between sequential scans are then precisely aligned using rigid registration. AIQ's articulated registration accounts for both global flexibility of skeleton and local rigidity of individual bones.[8]

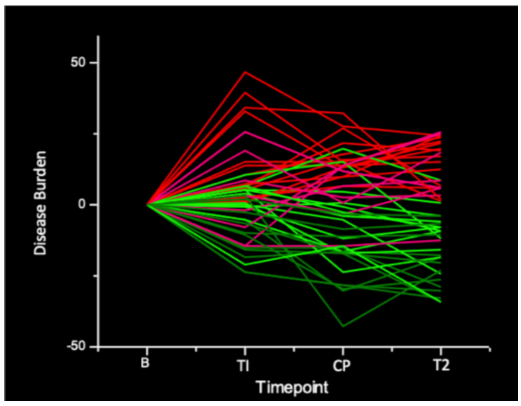
F. **Automatic Lesion Matching**: Corresponding lesions are automatically matched between sequential scans according to the bone alignment resulting from articulated registration. The technology automatically adjusts for situations where lesions have combined or split in the time between scans and identifies development of new lesions and disappearance of lesions.

G. **Automatic Treatment Response Assessment**: Treatment response is calculated for each individual lesion as the change in disease burden from one scan to another scan acquired at later timepoint.[9]

H. **Automatic Response Classification**: Treatment response is classified as "responding," "stable," or "progressing." Data from test-retest analysis were used to determine the inherent variability in disease burden measurement for a specific anatomical region. These were used to calculate whether a measured change in disease burden exceeds the target confidence interval. If so, the lesion is classified as either "responding" for a decrease in disease burden or "progressing" for an increase.

I. **Treatment Response Report**: Final results are stored in a secure cloud-based database, allowing customer access for subsequent analysis and interpretation. Figure 2 shows an example of the temporal and spatial data returned for each lesion on a single patient

A.



B.

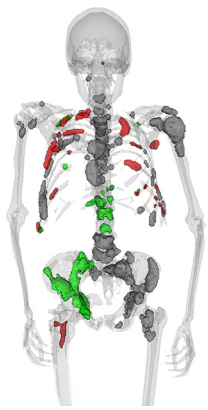


Figure 2. (A) The graph represents the quantitative response metrics at different times for every lesion based on changes in SUVtotal (Disease Burden). Each line represents a lesion at Baseline (B), Time 1 (T1), Clinical Progression (CP), and Time 2 (T2). **(B)** The image on the right, represents the precise location of the lesions in the right graph, combined with the response status for each lesion.

Technology Validation

The robustness of AIQ's underlying technology, applied to ^{18}F-NaF PET/CT scans, was established in a multi-site clinical trial wherein 411 lesions from 35 metastatic castration-resistant prostate cancer (mCRPC) patients were analyzed in a test-retest protocol.[10] The study compared three different metrics of disease burden: SUV_{max}, SUV_{mean}, and SUV_{total}. The relative differences between quantified values in the test-retest, considering both individual lesion and composite patient analysis, are shown in Figure 3. The intraclass correlation coefficient was >0.95 for all metrics (an ICC of greater than 0.75 is considered excellent repeatability), establishing the robustness of results generated by the AIQ's technology.

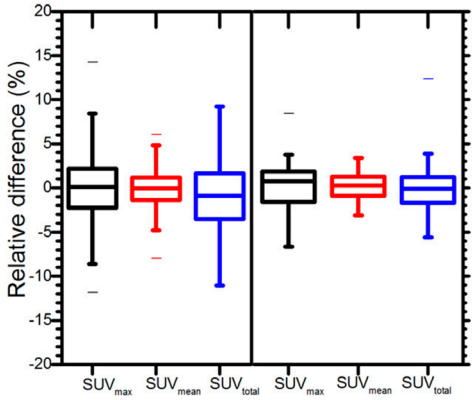
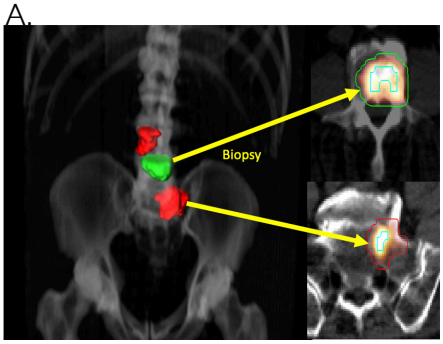


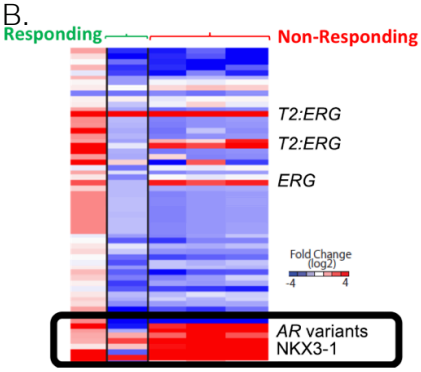
Figure 3. Box plots of relative differences in each SUV metric (log-transformed) for lesion-level ROIs (left; 411 lesions) and patient-level ROIs (right; 35 patients). Whiskers extend from minimum to maximum values.

The technology platform was further validated biologically through analysis of molecular data derived from tumor biopsies. Patients with mCRPC receiving androgen receptor axis-targeting therapies (AATTs) were analyzed using AIQ's TRA procedure, including classification of lesions as "responding," "stable," or "progressing." From the spatial information provided, researchers selected pairs of lesions that were proximately located and exhibiting different treatment responses (see Figure 4). Biopsy samples were taken from each pair and the mRNA was analyzed. The results found androgen receptor splice variant V7 (AR-V7) in progressing lesions, but not in the lesions classified as responding or stable.[11] The AR-V7 has been identified as a biomarker for resistance to AATTs,[12] thus this evaluation serves as biological validation for the TRA's identification and classification of lesions.

A.



B.



C.

Pt	Lesion Response Classification	AR-V7	AR-V1,V3,V4	AR-V3	AR-V9
3	PR	Negative	Negative	Positive	Negative
3	PD	Negative	Negative	Positive	Negative
4	SD	Negative	Negative	Negative	Negative
4	PD	Positive	Positive	Positive	Positive
5	PR	Negative	Negative	Positive	Positive
5	PD	Positive	Positive	Positive	Positive
6	PD	Positive	Positive	Positive	Positive

Figure 4. (A) The TRA procedure identifies two proximate lesions, one that has been classified as "responding" and the other that has been classified as "progressing." (B) Quantitative mRNA analysis of the paired lesions shows differences between the "responding" and "progressing" lesions. (C) Further analysis shows that only "progressing" lesions express AR-V7.

Conclusions

AIQ's technology platform provides clinicians and researchers alike with actionable intelligence about intra-patient heterogeneity of treatment response. By combining quantitative spatiotemporal heterogeneity metrics for each lesion with its anatomical location, the technology provides information that would otherwise be impractical to obtain.

Clinical studies have established the robustness and biological validation of the AIQ platform, clearly demonstrating the great promise it holds for improving patient management and drug development efficiency.

References

1. Harmon SA, Perk T, Lin C, et al. Quantitative assessment of early [18F]sodium fluoride positron emission tomography/computed tomography response to treatment in men with metastatic prostate cancer to bone. *J Clin Oncol*.2017;35(24):2829-2837.
2. Vanderhoek M, Juckett MB, Perlman S, et al. Early assessment of treatment response in patients with AML using [18F]FLT PET imaging. *Leuk Res*. 2011;35(3):310–316.
3. Rasche L, Chavan S, Patel P, et al. Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing. Nat Commun. 2017;8(1):268.
4. Morgan G, Walter B, Davies F. The genetic architecture of multiple myeloma. *Nat Rev Cancer.* 2012; 12(5):335-48.
5. Rasche L, Alapat D, Kumar M, et al. The presence of large focal lesions is a strong independent prognostic factor in multiple myeloma. *Blood*. 2018:132:59-66.
6. Perk T, Chen S, Harmon S, et al. A statistically optimized regional thresholding method (SORT) for bone lesion detection in 18F-NaF PET/CT imaging. *Phys Med Biol*. 2018;63(22).
7. Perk T, Bradshaw T, Chen S, et al. Automated classification of benign and malignant lesions in 18F-NaF PET/CT images using machine learning. *Phys Med Biol.* 2018;63(22).
8. Yip S, Perk T, Jeraj R. Development and evaluation of an articulated registration algorithm for human skeleton registration. Phys *Med Biol*. 2014;59(6):1485-1499.
9. Yip S, Jeraj R. Use of articulated registration for response assessment of individual metastatic bone lesions. *Phys Med Biol*. 2014;59(6):1501-1514.
10. Lin C, Bradshaw T, Perk T, et al. Repeatability of quantitative 18F-NaF PET: a multicenter study. *J Nucl Med*.2016;57(12):1872-1879.
11. Roth A, Tomlins SA, Tuite M, et al. Targeting differential response using molecular guided biopsies in bone-metastatic prostate cancer. *J Clin Oncol* 2019;37(suppl; abstr e16516).
12. Zhang T, Karsh LI, Nissenblatt MJ, Canfield SE. Androgen Receptor Splice Variant, AR-V7, as a Biomarker of Resistance to Androgen Axis- Targeted Therapies in Advanced Prostate Cancer. *Clin Genitourin*.2020;18(1):1-10.