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Envita's Precision Cancer Care: 35-Fold Improvement in Response Rates

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Abstract

New clinical approaches are imperative beyond the widely adopted National Comprehensive Cancer Network (NCCN) guidelines, utilized by prominent cancer institutions. Cancer is the leading cause of death among individuals younger than 85 years within the United States. Despite significant technological advances, including the expenditure of hundreds of billions, treatment outcomes and overall survival have not notably improved for most types of advanced cancer over the last several decades. Over the past 24 years, Envita Medical Centers has pioneered a unique form of personalized treatment approach for late-stage and refractory cancer patients, introducing groundbreaking innovations in the field. Our integrated algorithm utilizes advanced genomics, transcriptomics, and highly tailored immunotherapy, resulting in remarkable outcome improvements. This study presents Envita's innovative personalized treatment algorithms and examines the response outcomes of 199 late-stage cancer patients treated at Envita Medical Centers over a two-year period. Compared to standard of care and palliative chemotherapy, Envita's treatment demonstrated a remarkable 35-fold improvement in overall response rates (Figure 1). Moreover, 88% of the patients, the majority presenting with Stage 3 or 4 cancer, experienced a 43-fold improvement in quality of life with minimal side effects, as compared to standard of care chemotherapy and palliative care. This revolutionary success is attributed to Envita's personalized therapeutic algorithms, which incorporate customized immunotherapy. Envita's precision care approach has also achieved a 100% better response rate compared to over 65 global chemotherapy clinical trials with more than 2700 patients. The results from this study suggest that a wider utilization of Envita's personalized approach can significantly benefit patients with late-stage and refractory cancer.

Keywords

Envita Medical Centers, Late-stage Cancer, Overall Response Rate, Quality of Life, Circulating Tumor Cells (CTCs), Mutant Allele Frequency (MAF), Precision Care

1. Introduction

Cancer is expected to impact over two million individuals within the United States in 2024, claiming more than 600,000 lives [1]. Traditional cancer treatment has primarily focused on cancer type, stage, and the affected organ. Chemotherapy regimens are predominantly governed by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines, which provides recommendations for diagnosing and managing malignancies throughout the continuum of care [2]. This approach has been adopted by all major cancer centers in the United States. These chemotherapy regimens (based mainly on cancer type, stage, and the affected organ) remain the most common form of treatment strategy; this standard chemotherapy approach has ensued in drug resistance and toxicity [3] [4].

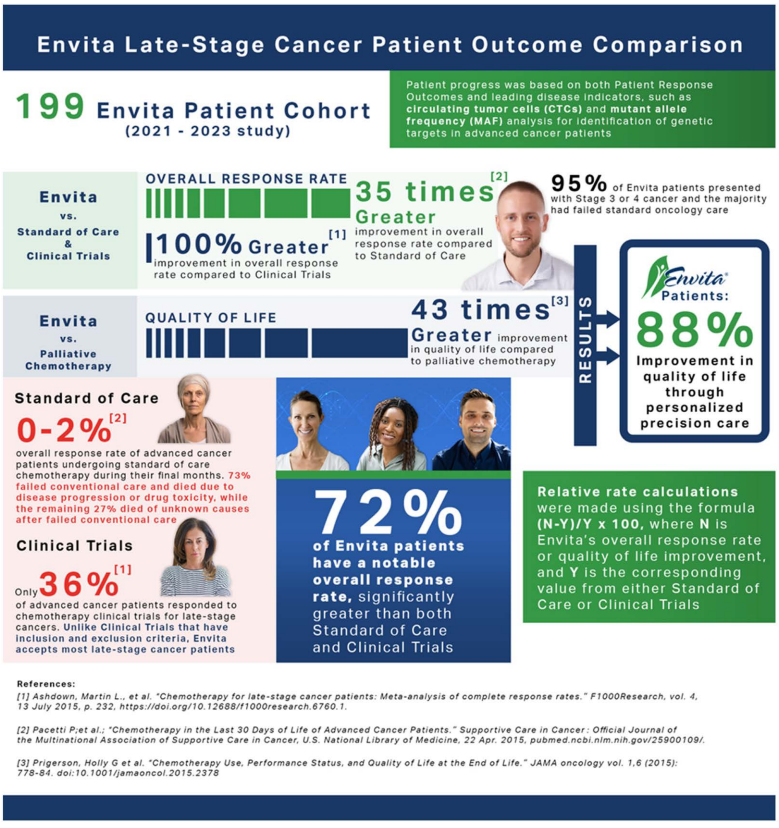

Figure 1. Envita's comprehensive outcome analysis for 199 patients demonstrates superior efficacy compared to standard oncology protocols and clinical trials, with a meticulous assessment of patient-reported quality of life metrics.

Despite significant technological advances in the field of molecular genetics, sequencing, and better understanding of molecular pathways, metastatic processes, and immunotherapy, the complete response rate has not improved for most advanced solid cancers over several decades; this rate for most patients with late-stage cancer remains at a low 5% - 10% [5]. These low response rates are attributed to tumor heterogeneity, resistance, and drug toxicity [5] [6].

One of the most revolutionized advances in modern oncology, attributed to next generation sequencing and the use of multi-omic approaches, has been the deep molecular analysis of localized and metastatic tumors and has provided the backbone for personalized medicine [4]. Longitudinal genome profiling in collaboration with multi-omic approaches can guide combinatorial treatments to overcome tumor heterogeneity and drug resistance as well as personalize drug administration [7]. Regular biomarker analysis, together with the identification of druggable molecular targets in primary and metastatic disease has the potential to dictate precision personalized care and facilitate treatment of dynamically mutating tumors [4]. Additionally, the inclusion of adjuvant integrative natural therapeutics provides a less toxic chemotherapy source and can favorably impact transcriptomics and multi-drug resistance [8]. Most chemotherapeutic drugs harbor significant toxicity and side-effects primarily due to lack of drug specificity and untargeted drug delivery [9].

Envita Medical Centers is one of the very few, if not only, centers of excellence offering precision personalized treatment to patients with advanced and complex cancers. With over 24 years of experience in treating patients with late-stage cancer, Envita's personalized treatment algorithms are driven by the latest technological advances in dynamic molecular profiling of localized and metastatic disease and strategies to overcome multi-drug resistance (**Figure 2**). Proprietary genetically targeted fractionated chemotherapy (GTFC), created at Envita's in-house Vertisis Custom Pharmacy, is then utilized to deliver low-dose fractionated chemotherapy targeting 7 - 10 genetic biomarkers. Additionally, Envita employs a holistic approach comprising GTFC, immunotherapy, direct to tumor chemo-immuno precision injections (CIPI) and adjuvant natural agents, and lifestyle changes to enhance cancer prognosis and reduce resistance in patients with late-stage cancer, most of whom have failed standard oncology care previously. Envita's innovative personalized cancer treatment algorithms, utilizing genomics, transcriptomics, and tailored immunotherapy, have significantly outperformed standard oncology care for Stage 3 and Stage 4 cancers.

Envita Medical Centers also employs a cutting-edge, multi-faceted approach encompassing three distinct response criteria to meticulously and dynamically monitor its patients' treatment outcomes and strategize care. Patient response criteria include patient-reported outcomes (PROs), the detection and enumeration of circulating tumor cells (CTCs), and the critical assessment of mutant allele frequency (MAF). This comprehensive strategy, as described in the current analysis, not only ensures precision in patient monitoring but also facilitates a personalized care paradigm, integrating gene mutation-drug matching capabilities.

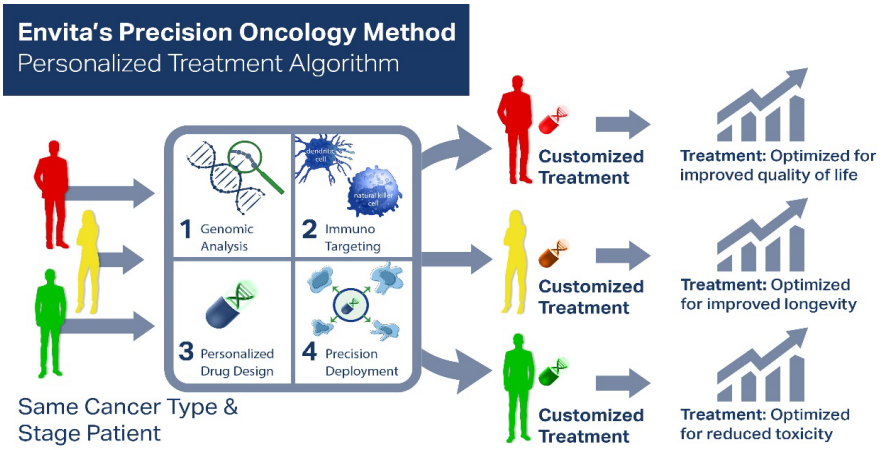

Figure 2. Diagram depicting Envita's advanced personalized precision oncology algorithm, meticulously designed to tailor treatment strategies based on individual (N of 1 treatment) patient characteristics and tumor biology.

2. Methods

This study elaborates the methods employed and the exceptional response outcome for advanced cancer patients treated at Envita utilizing our innovative and constantly improving personalized precision care algorithms. Envita's unique treatment strategy is guided by monitoring patient response outcomes (PROs) and leading indicators of disease, circulating tumor cells (CTCs) and mutant allele frequency (MAF), with predictive and prognostic value. Recognizing the limitations of relying on a single patient response criterion, especially as more advanced diagnostic and analytical tools emerge, our algorithms emphasize the importance of longitudinal personalized testing. Such an approach is particularly valuable in treating aggressive disease and optimizing the quality of care.

2.1. Patient Cohort

This study compiles the response outcomes for 199 late-stage cancer patients receiving over 70 days of care at Envita Medical Centers, with an average and median duration of 148 and 114 days, respectively, between 2021 and 2023. The majority of these patients had previously failed standard oncology care and thereby represented an extremely challenging cohort to treat. Envita obtained written consent from its patient cohort and ensured rigorous de-identification of their information before reporting outcomes.

Compared to clinical trials where inclusion and exclusion criteria are established for study participants, Envita is capable of treating the majority of Stage 3 and 4 cancer patients using our personalized algorithms and high standard of personalized care. Inclusion criteria for clinical trials typically include clinical, demographic, and geographic requirements that enable investigators to pick participants from a target population; exclusion criteria preclude participants that could cause the study to fail and thus may bias the results [10].

2.2. Response Outcomes

Patient response outcomes (PROs) and leading disease biomarkers, circulating tumor cells (CTCs) and mutant allele frequency (MAF), were measured for each patient at the onset and conclusion of cancer treatment. The rationale for using these response outcomes was to monitor and enhance the patient's quality of life as well as to use leading disease indicators to guide therapeutic strategies for enhancing patient longevity and quality of life. These response outcomes are described in more detail below.

A. Patient Response Outcomes (PROs)

Patient-Reported Outcome (PRO) is a subtype of Clinical Outcome Assessment (COA) that empowers patients to directly contribute to their health assessment, quality of life, and response to optimal medical therapy, offering a comprehensive evaluation of treatment effectiveness [11]. Integral to health-related quality of life (HRQoL), PROs serve as primary or secondary outcomes post-treatment, aiding patients and clinicians in informing future clinical decisions [11] [12]. These patient-completed questionnaires, recognized as identifiable, valid, and reliable patient-reported outcome measures (PROMs), encompass health-related quality of life, symptom burden, personal care experience, and behavioral impact [11]. While PROMs may be generic or disease-specific, the former focuses on self-care and mobility, while the latter identifies specific symptoms and their functional impact [11] [12]. Clinical studies often leverage a combination of both approaches [11].

For example, the EuroQol - 5-dimension (EQ-5D) questionnaire, a generic PRO measure developed by the EuroQol group, measures five aspects of healthcare, including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression across various diseases [13]. Two prevalent oncology-based PROMs include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy - General (FACT-G). The former comprises 30 items covering functional and symptom scales, global health status/QoL, additional symptom items, and a financial impact scale (eortc.org). The latter, FACT-G, focuses on physical, social, emotional, as well as functional well-being in cancer patients and is a 27-item questionnaire [14] [15].

The Envita PRO score questionnaire, scored directly by the patient, includes an evaluation of symptoms commonly observed in cancer patients such as physical assessment (fatigue, stamina, weight changes), neuropathies (pain, weakness, numbness), vision changes, neurological assessment (memory, dizziness, speech), gastrointestinal problems, cognitive function, sexual function, and mental issues (anxiety, depression) (**Figure 3**).

Envita's PRO score system, utilizing a 10-point Likert scale, aligns with health status and quality of life attributes identified by the Scientific Advisory Committee of the Medical Outcomes Trust. Envita's PRO score system was established under the guidance of Health Measures, the official information and distribution center for PROMIS, Neuro-QoL™, and NIH Toolbox®. This system is crucial in

Figure 3. Envita Pro Score Quality of Life questionnaire, scored directly by the patient, includes an evaluation of physical assessment (fatigue, stamina, weight changes), neuropathies (pain, weakness, numbness), vision changes, neurological assessment (memory, dizziness, speech), gastrointestinal problems, cognitive function, sexual function, and mental issues (anxiety, depression).

influencing clinical recommendations and aims to enhance progression-free survival (PFS), overall survival (OS), and patient quality of life, especially considering that 95% of Envita patients present with Stage 3 or Stage 4 disease. As a center of excellence for integrative and personalized medicine, the Envita PRO score system allows its medical staff *(extensively trained in personalized integrative oncology)* to evaluate treatment plans promptly and effectively, adapting therapeutic strategies as needed.

B. Circulating Tumor Cells (CTCs)

Circulating tumor cells (CTCs) are formidable indicators of cancer progression, representing tumor cells that have separated from the primary tumor or metastatic site, utilizing epithelial-mesenchymal transition (EMT) properties to enter the bloodstream or lymphatic system [16] [17]. Although many CTCs do not survive immune cells' assault, their EMT, stemness, and interaction with the blood environment potentially assists metastasis initiation at different sites [16] [18] (**Figure 4**). Recent technical advances in CTC isolation and characterization have facilitated their use for diagnostic, response monitoring, and prognostic purposes; CTC enumeration and characterization during treatment can rapidly

dictate tailored therapeutic strategies because these represent the tumor's molecular profile [19] [20] [21]. A high CTC count is associated with poor prognosis during disease detection or treatment [17].

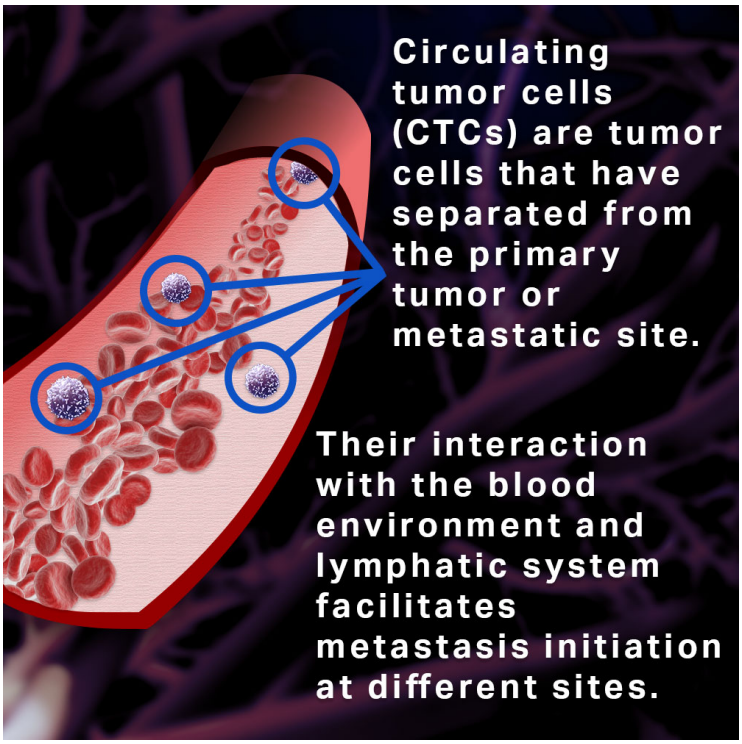

Figure 4. Circulating tumor cells and their significance in cancer cell biology.

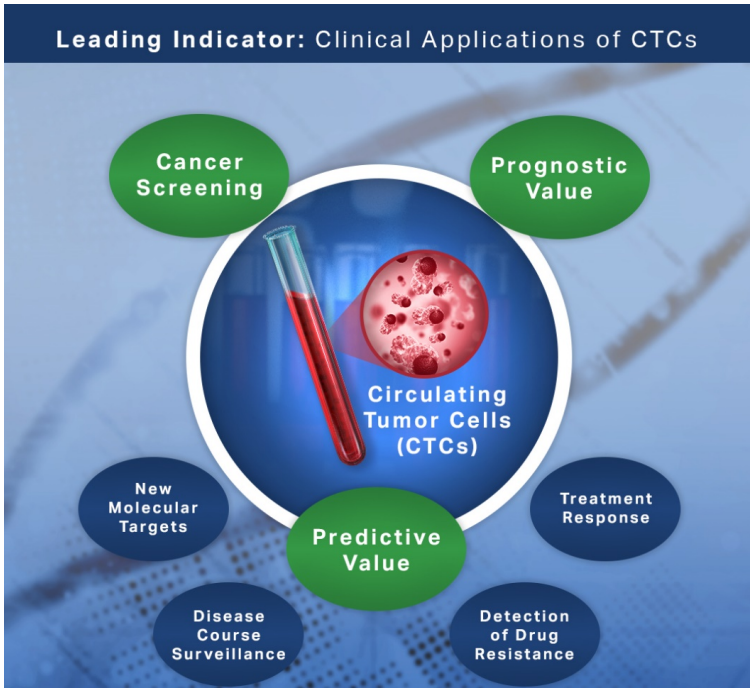

Figure 5. Clinical significance of circulating tumor cells (CTCs): Unlocking their pivotal role in cancer diagnosis, treatment, and prognosis.

Epithelial cell adhesion molecule (EpCAM), a universal epithelial marker, plays a crucial role in CTC detection. Although EpCAM is a valuable tumor marker for CTCs of epithelial origin, other markers are also employed for CTC detection [16]. EpCAM-based detection technologies may not be optimized for CTCs from mesenchymal cancers, necessitating additional markers for accurate detection [21].

CTC enumeration and detection provide several advantages compared to traditional technologies for early detection, metastasis, and prognosis of cancer; a CTC count of ≥5 CTC/7.5 mL of blood generally indicates metastatic disease [17]. CTCs, identified through liquid biopsy, provide non-invasive diagnostic and prognostic information; the presence of CTCs indicates a primary tumor and/or metastasis prior to other methods of clinical detection and enables molecular and genetic analysis of disease [18] [22] (**Figure 5**). Molecular and genetic analysis of CTCs enables targeted therapy, precision medicine, and personalized treatment strategies, aligning with biomarker status in primary and metastatic tissues [23] [24] [25].

CTC detection and enumeration for Envita patients were conducted using Datar Cancer Genetics, Fluxion Biosciences, Biocept, or Menarini Silicon Biosystems. Each laboratory utilized distinct isolation and enumeration techniques; the same laboratory was employed for longitudinal testing on a given patient. For example, Datar Cancer Genetics defined CTCs as CK+, EpCAM+, and CD45-cells, with further immunocytochemistry (ICC) analysis. Fluxion utilized a proprietary Isoflux Enhanced CTC enrichment kit using EpCAM and EGFR, while Biocept defined CTCs as CD45-, CK+ or CK-, DAPI+ cells, capturing CTCs with antibodies targeting multiple markers including EpCAM. Menarini Silicon Biosystems employed the CellSearch® Circulating Tumor Cell system. As per the CellSearch® system, patients with ≥5, 3, or 5 CTCs/7.5 mL of blood in metastatic breast, colorectal, or prostate cancer, respectively, had shorter overall and progression-free survival; changes in the number of CTCs during treatment were important predictors of prognosis.

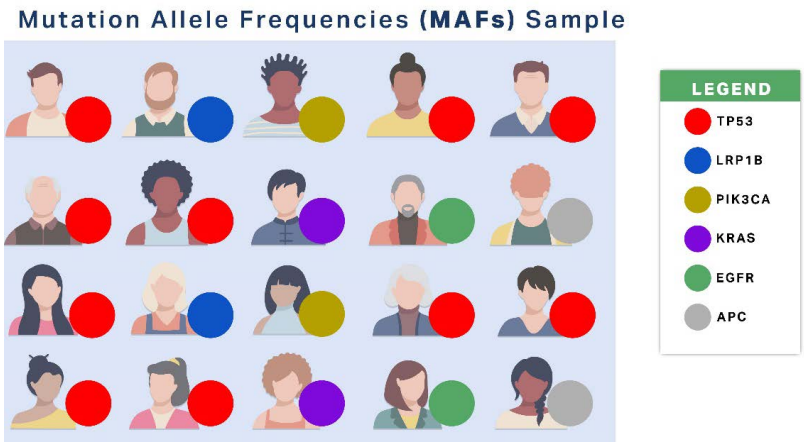

Figure 6. Examples of mutation allele frequencies (MAFs) observed in oncology treatment planning. The MAF value is unique for each patient.

C. Mutant Allele Frequency (MAF)

Circulating tumor DNA (ctDNA), derived from apoptosis and necrosis of tumor cells, comprises a subset of total circulating cell-free DNA (cfDNA) and is a molecular reflection of the entire tumor genome, making this blood-based biomarker superior compared to a tissue biopsy sample [26] [27]. Tumor-specific variants in cfDNA are measured using the mutant allele frequency (MAF), which is defined as the ratio of number of mutant DNA molecules to the total number of molecules containing the same allele [26] [28]. Accurate MAF quantification requires sensitive and specific methods for the detection and quantification of low ctDNA levels in cfDNA, which is guided both by experimental methods and bioinformatic tools [26]. This allows for the identification of actionable mutations that can be targeted to deliver precision medicine based on the specific genetic profile of the tumor for better outcome-based patient care [26] [29] (**Figure 6**). Higher MAF levels are associated with lower overall survival in advanced cancers; monitoring MAF levels also allows for early detection of relapse, determination of treatment response, and predict prognosis as well as overall survival [30] [31].

Mutant Allele Frequency (MAF) plays a crucial role in monitoring cancer outcomes due to its ability to provide insights into the genetic landscape, genomic diversity, and clonal evolution of tumors [32]. Tumors are often genetically heterogeneous consisting of various mutated cell populations. Intra-tumor heterogeneity presents an enormous clinical challenge because it causes metastasis and therapeutic resistance; MAF distributions have been used to determine tumor heterogeneity and hence predict patient outcomes [33] [34]. MAF quantification depends on the real-time status of genetic alterations within the tumor genome and reflects the proportion of mutant DNA molecules derived from primary tumor and metastasis present in ctDNA, providing a dynamic and global picture of tumor heterogeneity, a better representation compared to biopsy from a single solid tumor sample [26]. MAF analysis at Envita was conducted using semiconductor-based next-generation sequencing (NGS) targeting a panel of 461 genes or hybridization-based NGS in a panel of 317 genes.

2.3. Exclusion Criteria

Out of the 199-patient cohort, 77, 65, and 51 patients were excluded from the PROs, CTC, and MAF response data, respectively, due to the patient's inability to start or complete Envita's prescribed personalized oncology protocol. The reasons for excluding a patient from the analysis were attributed to (a) inability to start the protocol due to advanced disease, (b) liver and kidney complications, (c) travel, financial, or other limitations, (d) referral to hospice care because of disease progression, and (e) radiation and/or surgical complications.

2.4. Response Measurement

A "positive" or "negative" patient response was determined by a quantitative decrease or increase, respectively, in the response criteria at the end vs. start of

treatment by 30%; all other outcomes indicated a "stable" condition. Positive, negative, or stable responses for PROs, CTCs, and MAFs were calculated for each patient, and the respective percentages were determined for the entire patient cohort. All the statistical analysis was performed in Excel.

3. Results

The current analysis underscores the significance of obtaining prompt clarity on the effectiveness of a treatment plan, particularly for late-stage cancer where timely insights are crucial for making informed decisions and optimizing patient care. Swift identification of treatment response enables faster intervention, thereby aligning with the goal of extending patient life and enhancing overall outcomes.

Approximately 81% and 13% of patients coming to Envita presented with Stage 4 and Stage 3 disease, respectively, encompassing a diverse range of common and uncommon cancers, most of whom had previously failed standard of care. The types of cancers treated at Envita included colorectal, breast, pancreatic, prostate, gastric, gynecological, lung, kidney, neuroendocrine, bladder, peritoneal, appendiceal, cholangiocarcinoma, squamous cell carcinoma, and mesothelioma (Figure 7).

Many prognostic tests in cancer today serve as lagging indicators of disease and/or relapse, employing older technology that may not fully account for the advances in personalized cancer testing. Envita's analysis emphasizes the benefit of multimodal cutting-edge approaches to provide real-time and comprehensive assessments, ensuring that treatment decisions are based on the most advanced, as well as the most accurate and personalized information available in order to augment the patient's quality of life and maximize life expectancy. The results from each individual response parameter evaluated for this analysis are discussed below.

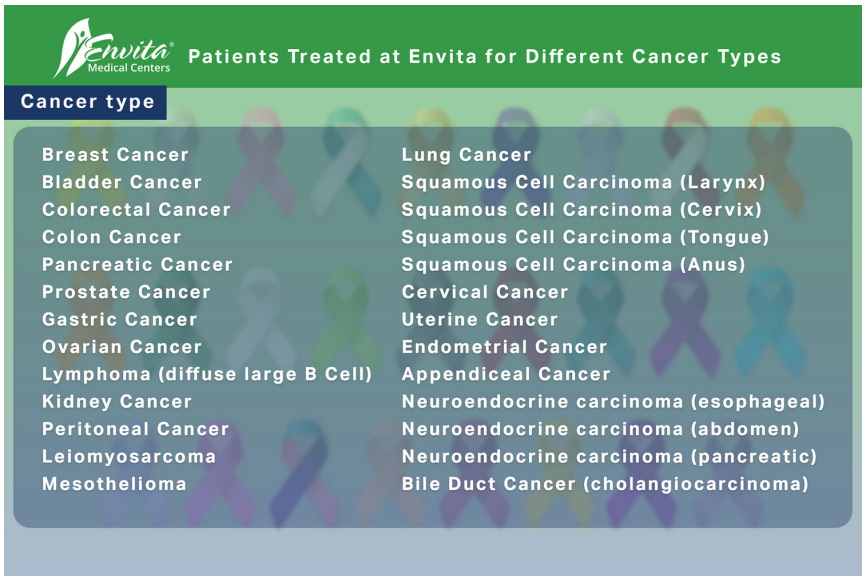

Figure 7. Patients treated at Envita for various types of cancer within a cohort of 199.

3.1. Patient Response Outcomes (PROs)

Among the 199 patients in this analysis, 77 patients were excluded from reporting PRO scores; a positive (decrease in PRO score), stable, and negative (increase in PRO score) response was observed in 68%, 21%, and 11% of patients, respectively, following treatment. A decrease in the patient's PRO score correlated with an improved quality of life. With a mean initial and final patient symptom score of 51 and 30, respectively, and a median initial and final score of 41 and 21, respectively, Envita's goal is to provide exceptional patient care through personalized integrative medicine, including immunotherapy, direct patient-specific tumor-targeted interventional radiology oncology therapy, low-dose or metronomic chemotherapy, targeted phytotherapeutics, oxidative medicine, nutraceuticals, dietary changes and health supplements. This continuous feedback loop involving direct patient response, effective clinical monitoring, and action is a testament to Envita's commitment to support its patients' needs and maintain their quality of life.

Most oncology clinics that provide palliative chemotherapy to late-stage cancer patients indicated that QoL scores deteriorated in this patient cohort; this is in stark contrast to Envita patients, 88% of whom experienced an overall symptom improvement and enhanced QoL [35] [36]. Patients treated at Envita experienced 43 times greater QoL enhancement compared to late-stage cancer patients undergoing palliative chemotherapy, assuming that the latter cohort experienced a 2% QoL improvement under the best-case scenario (Figure 8). Most Envita patients had previously failed late-stage cancer care at other oncology clinics and thereby constitute the most challenging cohort to treat. These impressive results are attributed to Envita's personalized treatment algorithms incorporating integrative precision targeted medicine based on molecular profiling of the cancer, immunotherapy, and metronomic chemotherapy doses delivered to its patients.

Figure 8. Envita patients experienced a 43-fold increase in quality of life (QoL) improvement compared to late-stage cancer patients undergoing palliative chemotherapy. This enhancement assumes a 2% QoL improvement in patients undergoing palliative chemotherapy under the best-case scenario. Additionally, Envita patients benefit from a 100% precision treatment strategy compared to standard oncology care.

3.2. Circulating Tumor Cells (CTCs)

CTC detection and enumeration were conducted using Datar Cancer Genetics, Fluxion Biosciences, Biocept, or Menarini Silicon Biosystems for Envita patients. A positive or negative patient CTC score was characterized by a 30% or more decrease or increase in the final CTC value compared to the initial value, respectively; all other results were considered stable. Out of the 199 patients, 65 were excluded, 32%, 39%, and 29% of patients showed positive, stable, and negative responses, respectively. Despite approximately 95% of Envita's patients being in Stage 3 or 4, CTC levels, combined with MAF biomarker analysis, effectively determined treatment plans and therapeutic strategy adjustments, exemplifying superior patient care with enhanced longevity and quality of life.

3.3. Mutant Allele Frequency (MAF)

MAF is increasing being used in clinical decision-making as a biomarker for treatment response; changes in MAF over time and molecular profiling of the ctDNA can indicate an early response of tumors to treatment as well as acquired resistance mechanisms [31]. A decrease in MAF may suggest a positive response, while an increase could indicate resistance or disease progression. CtDNA sequencing not only provides a clinical diagnosis but also aids in the discovery of new mutations, providing appropriate personalized treatment strategies and patient prognosis [26].

MAF analysis at Envita was conducted using semiconductor-based next-generation sequencing (NGS) targeting a panel of 461 genes or hybridization-based NGS in a panel of 317 genes. Out of the 199 patients at Envita, 51 were excluded; 46%, 27%, and 27% of the remaining patients showed a positive, stable, and negative response, respectively, in terms of MAF levels. MAF analysis in combination with CTC levels were used to determine therapeutic strategies for enhanced patient care at Envita.

4. Discussion

Patient progress at Envita was effectively monitored using patient response outcomes (PROs) as well as leading disease indicators including circulating tumor cells (CTCs) and genomic targets identified by measuring the mutant allele frequency (MAF); these measures resulted in a notable overall patient response rate of 72%. Envita's treatment has shown a remarkable 35-fold improvement in overall response rates compared to standard of care. Moreover, 88% of our patients, the majority presenting with Stage 3 or 4 cancer, experienced a 43-fold improvement in quality of life with minimal side effects, as compared to standard of care chemotherapy and palliative care. This revolutionary success is attributed to our personalized therapeutic algorithms, which incorporate customized immunotherapy. Envita's precision care approach has also achieved a 100% improvement in overall response rates compared to over 65 global chemotherapy clinical trials with more than 2700 patients [5].

Different cancer standard of care treatments, such as chemotherapy, immunotherapy, radiation, hormonal therapy, and their combinations, is associated with significant side effects impacting the patients' quality of life [37]. While overall and disease-free survival remains critical in cancer care, quantifying Patient-Reported Outcomes (PROs) provide a comprehensive assessment of cancer burden and intervention impact, guiding effective patient and clinical decision-making to improve care quality [37]. For instance, studies assessing Health-Related Quality of Life (HRQoL) in cancer patients emphasize the importance of early supportive care, showing potential symptom relief and improved HRQoL scores [38]. Another study demonstrates that systematic symptom reporting in cancer patients, leading to timely intervention, positively impacts HRQoL scores, reducing hospitalizations and emergency room visits, thereby enhancing quality-adjusted survival and cost of care reduction [39].

Palliative chemotherapy to control symptoms and maintain or improve QoL is essential for patients with advanced disease that is refractory to treatment [40]. Although 20% - 50% of patients with advanced cancer receive chemotherapy towards the end of life, palliative chemotherapy has been associated with cardiopulmonary resuscitation and/or mechanical ventilation, late hospice referrals, additional costs and suffering to patients without a difference in survival [41] [42] [43]. For instance, data from eight outpatient oncology clinics suggested that the 216 (56%) of the 386 terminally ill cancer patients receiving palliative chemotherapy were more likely to receive cardiopulmonary resuscitation, mechanical ventilation, feeding tubes, and late hospice referrals with no change in overall survival; these patients were also more likely to not die in their preferred place [41]. In a multi-institutional study comprising 158 patients who received palliative chemotherapy prior to death, chemotherapy use did not improve quality of life near death (QOD) for patients with moderate to poor performance status and deteriorated QOD for patients with good performance status [36]. Patients (104) with metastatic cancer receiving palliative chemotherapy had significantly different EORTC QLQ-C30 scores of 20 points or more compared to healthy controls for majority of the QoL domains including appetite, fatigue, role functioning, dyspnea, physical and social functioning, global QoL, pain, and nausea [40]. The EORTC QLQ-C30 scores were significantly different for emotional and social functioning as well as for financial impact in patients undergoing third+ line vs first line chemotherapy [40]. In another study with 187 lung cancer patients, QoL scores reported using EORTC QLQ-C30 remained stable during treatment for each chemotherapy line but the second and third+ line palliative chemotherapy lines were associated with high symptom burden and worse QoL scores; third or above line palliative chemotherapy resulted in the worst QoL scores [44].

Out of the 199 patients at Envita, 65 were excluded, 32%, 39%, and 29% of patients showed positive, stable, and negative responses for CTCs, respectively. CTCs serve as predictors of treatment response and survival, especially when tissue biopsy is impractical [18] [45]. For instance, the prostate specific antigen

(PSA) test may result in overdiagnoses, resulting in an invasive tissue biopsy and overtreatment; CTC analysis enhanced prediction of clinically significant prostate cancer when combined with PSA and/or multiparametric magnetic resonance imaging for biopsy and treatment [46].

CTCs are leading indicators of disease with high diagnostic accuracy and may provide improved reproducibility with better correlation to overall survival compared to imaging [20] [47]. For instance, Budd and coworkers (2006) demonstrated that for 138 metastatic breast cancer patients, interreader variability for radiology and CTC counts was 15.2% and 0.7%, respectively. The median overall survival for patients with ≥ 5 CTCs/7.5 mL blood was significantly shorter compared to patients with < 5 CTCs/7.5 mL blood, irrespective of radiologic progression [20]. CTC counts also provided prognostic information for patient stratification and tailored therapeutic selection in patients with metastatic breast cancer; CTC count was a robust prognostic marker in the overall population but not in patients with human epidermal growth factor receptor-2-overexpressed tumors [48]. Additionally, a baseline CTC ≥ 5 CTCs/7.5 mL blood identified patients who would benefit from more aggressive treatments for human epidermal growth factor receptor-2 normal tumors [48].

Out of the 199 patients at Envita, 51 were excluded; 46%, 27%, and 27% of the remaining patients showed a positive, stable, and negative response, respectively, in terms of MAF levels. MAF levels have prognostic significance and can independently predict patient outcomes. Higher MAF has been associated with lower overall survival in patients with metastatic disease [31]. For instance, high MAF levels of TET2 and TP53 were independently associated with shorter overall survival in patients with myelodysplastic syndromes [49]. Studies have also shown that MAF for different mutations was associated with response to treatment and could be used to evaluate patients early for recurrence, thereby allowing for clinical intervention and improving patient outcomes [32]. MAF levels have also been linked to progression time and determining disease progression; monitoring changes in MAF levels aids in assessing the aggressiveness and evolution of the disease [29].

The TP53 tumor suppressor regulates molecular pathways of apoptosis, DNA repair, senescence, and cell cycle arrest in response to DNA damage. TP53 is the most frequently altered gene in human tumors; most TP53 mutations are missense and responsible for aberrant signaling of cellular pathways, enhanced proliferation, oncogene amplification, metastasis, and chemoresistance [50] [51]. Mutant p53 also promotes tumor progression by altering the cellular metabolism and facilitating adaptive responses to cancer-related stress conditions [50]. Belickova *et al.* (2016) analyzed the MAF for each TP53 mutation detected in patients with myelodysplastic syndrome and determined that a 6% MAF was optimum for outcome prediction. The overall and progression free survival for patients with a MAF > 6% for a TP53 mutation at the time of diagnosis was significantly shorter compared to patients with a MAF < 6% at the time of diagnosis or patients without the mutation [52]. Similarly, a MAF

≥ 10% in patients with TP53-mutated myeloid neoplasms had significantly shorter survival compared to patients with wild type TP53 and patients with MAF < 10% [53].

Given that most of our patients are not Arizona residents and may have undergone imaging at various locations, in addition to the short treatment duration at Envita renders imaging and tumor markers as unreliable biomarkers for our patient outcome assessment. Tumor response following treatment is commonly assessed using imaging techniques; response evaluation criteria in solid tumors (RECIST) and positron emission tomography (PET) response criteria in solid tumors (PERCIST) have been the established morphologic and metabolic response criteria to predict outcomes and dictate treatment [54]. Immunotherapy often causes the tumor to increase followed by a decrease, a phenomenon known as "pseudoprogression", discrediting the use of computed tomography or magnetic resonance imaging for evaluation [54] [55]. An immune response can also cause 18F-fluorodeoxyglucose (FDG), used as a diagnostic radioactive tracer for PET, uptake in tumors thereby invalidating the use of FGD-PET imaging for follow-up after immunotherapy [54].

Tumor markers were not used as response predictors because these are lagging indicators of disease; their levels may spike following treatment [56]. For instance, levels of CEA (carcinoembryonic antigen) and CA 15-3 (cancer antigen 15-3) in patients with HER2-negative breast cancer spiked immediately following chemotherapy and decreased three months post chemotherapy; the increase was attributed to chronic inflammation and metabolic changes during chemotherapy [56]. CEA and CA 19-9 (carbohydrate antigen 19-9) levels transiently spiked following chemotherapy in patients with metastatic or recurrent gastric cancer, despite evidence of benefit from treatment [57]. Additionally, tumor markers such as CEA, CA 19-9, CA 15-3, cancer antigen 125 (CA 125), and cancer antigen 27-29 (CA 27-29) may be non-specific markers that are overexpressed in certain benign and malignant conditions [58] [59].

5. Limitations

While our dedication to refining therapeutic personalized algorithms persists alongside technological developments and available data, it is crucial to acknowledge the obstacles posed by institutional biases and regulatory constraints impeding expedited progress toward optimal enhancements in personalized medicine outcomes and recognizing that these advances may not benefit all patients. Nevertheless, Envita's unparalleled algorithm and methodology have demonstrated remarkable efficacy and potential. By incorporating dynamic response parameters, we achieve a profound comprehension of patient-specific intricacies, facilitating the monitoring of disease progression and tumor response to therapy nuances. This personalized integrative strategy, bolstered by longitudinal testing, has been pivotal in tailoring precise, individualized interventions, thus enhancing the treatment standard for Envita's patients.

6. Conclusions

Although it is difficult to obtain overall response rates for patients with advanced stage cancer undergoing standard oncology care, the objective response rates for clinical trials often exceed the actual clinical data [60]. In fact, the complete clinical response rate for advanced solid cancers irrespective of the type of therapy is as low as 5% - 10% [61]. Data for advanced cancers treated using standard chemotherapy is limited; studies have suggested that approximately 73% of advanced stage cancer patients undergoing chemotherapy during the last month of their life died from disease progression, toxicity, or suddenly while the cause of death for the remaining 27% was not available [35]. Considering this to be an approximate 0% - 2% response rate (because there were no surviving patients), Envita's overall response rate of 72% is approximately 35 times improved compared to late-stage standard of care [35]. Our quality of life improvement is approximately 43 times better compared to patients undergoing palliative chemotherapy [36]. The impact of our outcomes is further highlighted when considering that most of these 199 Envita patients had previously failed cancer treatments at other oncology clinics and comprised a hospice or palliative care patient cohort. We anticipate that these patients could have further benefited from our novel therapeutic algorithms had they sought treatment at Envita earlier during the disease course.

Envita's N of 1 treatment strategy to address its patients' oncology needs is a major step towards providing individualized precision therapy which can provide immediate benefit to the patient because most have failed care at other oncology clinics and are almost at the end of life. The N of 1 method used by Envita is especially important for the patient and treating physician; it has the potential of stratifying patients based on their cancer's molecular profile to optimize treatment [62]. The realization that a particular medical intervention does not work for the majority of common chronic conditions has underscored the importance of genetic testing for better patient outcomes and individualized care [62]. Factors that impact a patient's response to therapy include differential drug absorption, distribution, metabolism, and excretion at the organ, tissue, cellular, and molecular levels, and several drug companies such as Bristol-Myers Squibb, Roche Holding Ltd., and Novartis AG are using gene markers to make drug delivery more effective for patients with a specific genetic make-up [63] [64]. The National Institute of Health (NIH) strongly advocates utilizing advanced molecular techniques such as DNA sequencing, proteomics, and metabolomics for revolutionizing health care with the intent of matching known cancer targets with specific therapeutics [65].

Several reports have suggested that treatment outcomes and overall survival have not changed significantly for most types of advanced cancer over the last several decades [5] [66]. Data from clinical trials have indicated that approximately 65% of late-stage cancer patients are non-responders [5]. Meta-analysis of 68 chemotherapy trials (2732 patients) showed that complete response for

late-stage cancer chemotherapy regardless of cancer type and drugs used was a dismal 7.4% and partial response was a mere 28.1% [5]. The patients included in this study at Envita comprise a challenging cohort because most have already failed standard oncology care at other institutions, and the majority would be sent to hospice or palliative care. Envita's impressive results can be attested by the fact that approximately 72% of Envita patients experienced a positive or stable response to treatment as indicated by the combined CTC and MAF values measured at the beginning and end of treatment. This corroborates with an 88% improvement in the quality of life; Envita's results would further improve if patients sought treatment at Envita earlier in the process.

At the core of our patient care strategy is the implementation of a state-of-the-art, blood-based liquid biopsy and unique drug and treatment design. This revolutionary molecular testing, seamlessly integrated into our patient care framework, stands as a testament to our commitment to efficiency and excellence. The rapid testing and prompt feedback derived from this liquid biopsy not only streamlines our diagnostic processes but also significantly contributes to the enhancement of overall care quality for every patient under the care of Envita Medical Centers. Our unwavering dedication to the integration of advanced technologies ensures that our patients receive the highest standard of care, firmly establishing Envita as a vanguard in the pursuit of transformative and individualized medical solutions.

The findings from this analysis underscore the efficacy of Envita's continuously improving, personalized cancer treatment algorithms, which are uniquely tailored to each patient and focused on a N of 1 treatment methodology. Such positive outcomes should prompt a wider adoption of Envita's integrative personalized targeted therapeutic approach in oncology and insurance coverage by carriers.

7. Future Prospects

A critical question emerges: why are other oncology institutions lagging behind in adopting precision personalized medicine, despite its urgent demand? The obstacles are formidable: institutional bias, infrastructure limitations, insurance coverage restrictions, and reluctance to embrace new technology due to insufficient training in personalized targeting. However, we anticipate a paradigm shift driven by patient outcomes, catalyzing advances in technology and treatment.

This shift holds promise for improved matches for molecular targets, refined drug interactions, and accelerated drug discovery and delivery. Ultimately, these advancements have the potential to mitigate medical costs and revolutionize outcomes. The personalized tailoring of medical treatments, including both on and off-label medications and integrative agents, offers a highly promising approach. Notably, it presents a more cost-effective alternative to exclusive reliance on new drug development in patient care.

By integrating these methods, we envision exponential progress in oncology, paving the way for enhanced patient outcomes, cost reduction, and transforma-

tive advancements. Given its potential to significantly enhance patient outcomes, Envita's personalized integrated approach should be recognized as a pivotal component of the evolving personalized landscape of oncology.

Conflict of Interests

In the interest of transparency regarding potential conflicts, Dino Prato NMD, serving as the founder, researcher, and CEO of Envita Medical Centers, leads the initiative on personalized treatment modeling. Notably, all physicians at Envita contribute to algorithm design, a process that demands rigorous oversight and training to ensure impartiality and the highest standards of patient care.

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