Cancer Genetics and Epigenetics 2024, Vol.12, No.3, 144-156
http://medscipublisher.com/index.php/cge

Feature Review Open Access

Integrative Approaches for Predicting Treatment Response in Advanced Solid Tumors

Hui Xu
Tianjin Medical University Cancer Institute and Hospital, Hexi, 300210, Tianjin, China
Corresponding email: xuhui@163.com
Cancer Genetics and Epigenetics, 2024, Vol.12, No.3 doi: 10.5376/cge.2024.12.0017
Received: 28 Apr., 2024
Accepted: 30 May, 2024
Published: 13 Jun., 2024

Preferred citation for this article:
Xu H., 2024, Integrative approaches for predicting treatment response in advanced solid tumors, Cancer Genetics and Epigenetics, 12(3): 144-156 (doi: 10.5376/cge.2024.12.0017)

Abstract This study explores a comprehensive approach for predicting treatment response in advanced solid tumors, with a focus on the effectiveness of combining molecular, imaging, and clinical data to improve prediction accuracy. Emphasis was placed on the role of advanced computational models, including machine learning and artificial intelligence, in improving predictive capabilities. By integrating diverse data sources, these methods provide a comprehensive understanding of tumor biology and treatment response, ultimately leading to more personalized and effective treatment strategies. The significance of these comprehensive methods for research and clinical practice was also discussed, pointing out their potential to improve patient prognosis. The future directions include molecular analysis, advances in computational algorithms, collaborative research, and data sharing programs, all aimed at improving the accuracy and applicability of predictive models in precision oncology.
Keywords Integrative approaches; Predictive models; Advanced solid tumors; Precision oncology; Personalized treatment strategies

1 Introduction

Treatment response in advanced solid tumors is a critical factor influencing patient outcomes and overall survival rates. Advanced solid tumors, which include malignancies such as breast, lung, colorectal, and pancreatic cancers, are often characterized by their complex biology and resistance to conventional therapies. The heterogeneous nature of these tumors means that patients may exhibit vastly different responses to the same treatment regimen. This variability poses a significant challenge for oncologists who aim to personalize treatment plans to maximize efficacy and minimize adverse effects. Understanding the mechanisms underlying treatment response is essential for improving therapeutic strategies and patient care (Wheeler et al., 2020).

The complexity and heterogeneity of advanced solid tumors necessitate the use of integrative methods to predict treatment response accurately. Integrative approaches combine data from multiple sources, including molecular and genetic profiling, imaging techniques, and clinical data. These methods enable a more comprehensive understanding of the tumor biology and the factors influencing treatment outcomes. For instance, combining genomic sequencing data with imaging biomarkers and clinical variables can provide a multidimensional view of the tumor, facilitating more precise predictions of how it will respond to specific treatments (Uzilov et al., 2016). The integration of machine learning and artificial intelligence further enhances the predictive power of these methods by identifying patterns and correlations that may not be apparent through traditional analysis.

Despite the promise of integrative methods, several challenges remain in predicting treatment response in advanced solid tumors. One of the primary challenges is the heterogeneity of the data, which can vary widely in type, quality, and source. Standardizing these diverse data sets for meaningful analysis is a complex task. Additionally, the high-dimensional nature of the data, including genomic, proteomic, and imaging information, requires sophisticated computational tools and substantial computational resources (Davis et al., 2020). Ethical and privacy concerns also arise from the integration and sharing of patient data. Moreover, translating predictive models from research settings to clinical practice involves addressing issues of model validation, reproducibility,

and real-world applicability (Bulen et al., 2023). Overcoming these challenges is essential for the successful implementation of integrative predictive approaches in clinical oncology.

The aim of this study is to comprehensively summarize the current integrated methods for predicting treatment response in advanced solid tumors. By studying the latest advances in genome sequencing, proteomic analysis, imaging techniques, and clinical data integration, this study will highlight the advantages and disadvantages of these methods. We will also explore the application of these methods in clinical settings and their impact on treatment decision-making. In addition to summarizing the current status of integration methods, this study will also determine future research and development directions. This includes exploring emerging technologies, computing power, and algorithm improvements in the fields of molecular analysis and imaging, as well as the potential for collaborative research and data sharing. This study will discuss the impact of these advances on personalized healthcare and how to utilize them to improve the prognosis of patients with advanced solid tumors. By identifying key areas for future research, a roadmap is provided for researchers and clinicians to improve the accuracy and clinical practicality of integrated method predictions.

2 Current State of the Art

2.1 Molecular and genetic profiling

The rapid development of integrative genomic approaches has significantly advanced personalized cancer therapy. Uzilov et al. (2016) demonstrated an approach that combines whole-exome sequencing (WES) and single-nucleotide polymorphism (SNP) microarray genotyping to identify somatic mutations, copy number alterations, gene expression changes, and germline variants in tumors. Their study found that 91% of patients had actionable genetic alterations, significantly impacting treatment decisions and outcomes. This integrative method provides comprehensive genomic information, forming the basis for personalized treatment plans (Uzilov et al., 2016).

Sailer et al. (2019) extended this approach by combining whole-exome sequencing and transcriptome analysis in a cohort of patients with advanced and metastatic cancers. This integrative analysis identified clinically relevant genetic alterations in 39% of cases, with an additional 16% identified when RNA sequencing was added. This suggests that combining genomic sequencing with transcriptomic data provides a more comprehensive understanding of tumor molecular characteristics, improving the specificity and efficacy of treatments (Sailer et al., 2019).

Wheeler et al. (2020) conducted multi-platform analyses of cancer patients, including genetic and epigenetic abnormalities and tumor microenvironment assessments, to identify mechanisms behind exceptional treatment responses. Their research found that some cancer patients exhibited extraordinary responses to specific treatments, which were associated with synthetic lethal interactions and rare genetic lesions. These findings offer valuable insights for developing new therapeutic strategies and highlight the importance of comprehensive molecular analyses (Wheeler et al., 2020).

Genomic sequencing is not only used to identify mutations in tumors but also to discover new biomarkers. Biomarkers play a crucial role in predicting treatment responses and monitoring disease progression. For example, Liu et al. (2023) demonstrated that integrating multiple data sources and using machine learning algorithms significantly improved the accuracy of drug response predictions. This indicates the importance of discovering and applying biomarkers in personalized cancer treatment (Liu et al., 2023).

2.2 Imaging techniques

Radiomics is a technique that extracts quantitative features from medical images, providing crucial information for the diagnosis and treatment of tumors. Sun et al. (2018) developed a radiomic signature to assess tumor-infiltrating CD8 cells in patients undergoing immunotherapy. Their study showed that this radiomic biomarker was validated across multiple independent cohorts and demonstrated potential in predicting clinical outcomes. Specifically, they found that the radiomic signature accurately predicted the levels of tumor-infiltrating CD8 cells, supporting personalized immunotherapy (Sun et al., 2018).

Radiomics can also predict responses to other treatments. For instance, Chung et al. (2022) proposed an integrative clinical prediction model for triple-negative breast cancer patients receiving neoadjuvant chemotherapy. By integrating ultrasound findings with blood test results, they developed a comprehensive model that accurately predicted pathological complete response, guiding clinicians in treatment planning (Chung et al., 2022).

Integrating imaging data with molecular analyses can significantly enhance the accuracy of treatment response predictions. Imaging techniques provide spatial and temporal dynamics of tumors, while molecular analyses reveal the genetic and proteomic characteristics. The combination of these approaches allows researchers to understand tumor biology from multiple perspectives.For example, Davis et al. (2020) emphasized the importance of integrating imaging and molecular data to improve predictive models. They found that combining imaging data with genomic and transcriptomic data resulted in more accurate predictions of treatment responses. This finding highlights the importance of utilizing multiple data sources in future cancer research (Davis et al., 2020).

In practical applications, the integration of imaging and molecular data has shown great potential. Studies have demonstrated that combining these data types can enhance tumor staging accuracy, predict treatment responses, and monitor tumor changes during therapy. These advancements not only improve clinical decision-making precision but also provide new possibilities for personalized treatment.

2.3 Clinical data and patient characteristics

Clinical variables such as patient demographics, tumor stage, and previous treatment history play a crucial role in predicting treatment responses. Davis et al. (2020) emphasized the importance of integrating clinical data with molecular and imaging information to improve predictive models. They found that the inclusion of clinical variables significantly enhanced the accuracy of treatment response predictions. For example, patient age, sex, tumor size, and location provided additional context for predictive models, increasing their precision (Davis et al., 2020).

Patient lifestyle and comorbidities can also influence treatment responses. Factors such as smoking history, alcohol consumption, obesity, and diabetes may affect treatment outcomes. Integrating these clinical variables not only enhances predictive accuracy but also helps identify high-risk patients, guiding personalized treatment planning.

Electronic Health Records (EHR) are digital systems that record patient health information, including medical histories, diagnoses, treatment plans, and laboratory test results. Integrating EHR with molecular and imaging data provides researchers with comprehensive patient information, facilitating more accurate predictions of treatment responses.

Liu et al. (2023) demonstrated that combining clinical, molecular, and imaging data using machine learning algorithms significantly improved the accuracy of drug response predictions. They found that integrating EHR data with genomic, transcriptomic, and imaging data enhanced predictive model performance. This underscores the importance of leveraging multiple data sources in future personalized cancer treatments (Liu et al., 2023).Additionally, EHR integration enables real-time patient monitoring and dynamic treatment adjustments. By analyzing laboratory test results and imaging data recorded in EHRs, clinicians can promptly detect abnormalities during treatment, adjusting therapies to improve outcomes.

3 Integrative Approaches

3.1 Multimodal data integration

Multimodal data integration is of great significance in precision oncology as it can provide a comprehensive understanding of cancer biology and improve the predictive ability of treatment response. This machine learning method can integrate high-dimensional biomedical data, including co expression analysis, survival analysis, and matrix factorization. These methods successfully predicted post treatment responses by extracting salient features from tissue pathological images and combining gene expression and clinical data. Research has shown that this comprehensive analysis method is superior to traditional models with a single data source and can more accurately identify key features related to treatment response.

Additionally, Liu et al. (2023) utilized machine learning algorithms to integrate clinical, molecular, and imaging data, significantly improving the accuracy of drug response predictions. Their research highlighted the potential of data integration in personalized cancer treatment. By combining multiple data sources, the research team gained a comprehensive understanding of tumor characteristics and predicted individualized treatment outcomes, providing strong support for clinical decision-making (Liu et al., 2023).

The advantage of multimodal data integration lies in its ability to combine different types of data, such as genomic sequencing, imaging data, and clinical records, providing a more holistic characterization of the disease. This integration method not only improves the accuracy of predictive models but also identifies new biomarkers and therapeutic targets, advancing the field of precision medicine. By comprehensively analyzing various data, researchers can uncover the complex biological properties of tumors and develop more effective personalized treatment plans.

3.2 Computational models

The development of precise predictive algorithms is essential for understanding the complex biology of cancer and improving treatment outcomes. Silberberg et al. (2022) introduced a Pharmaco-Pheno-Multiomic (PPMO) integration approach to build predictive models of therapeutic responses in leukemia and ovarian cancer. This method combined multiple omics datasets with phenotypic and therapeutic response profiles, creating novel biomarker profiles that accurately predicted treatment responses. The success of this integrative method demonstrated the significant potential of comprehensive data analysis in cancer therapy (Silberberg et al., 2022).

Another important study by Halasz et al. (2016) developed a computational framework to identify network rewiring in colorectal cancer cells and predict resistance to EGFR inhibitors. Their research was validated not only in cell models but also in zebrafish tumor models. This study highlighted the application potential of network modeling in predicting personalized treatment responses and demonstrated that integrating network data could better understand mechanisms of drug resistance (Halasz et al., 2016).

The development of predictive algorithms relies not only on data integration but also on advanced computational methods and models. By combining machine learning and systems biology approaches, researchers can develop more accurate and robust predictive models, enhancing the effectiveness of personalized treatments. These models can predict patient responses to specific therapies and identify potential biomarkers and therapeutic targets, providing valuable guidance for clinical practice.

3.3 Systems biology approaches

Network-based methods are powerful tools for predicting treatment responses by modeling complex biological interactions. Rodin et al. (2022) emphasized the importance of integrating protein-protein interaction networks with regulatory networks to identify prognostic genes and regulatory mechanisms in cancer. Their approach provided new insights into tumor immune microenvironments and potential immunotherapy strategies by combining various biological network data. This method not only enhanced the predictive capability for treatment responses but also helped identify new therapeutic targets (Rodin et al., 2022).

Boehm et al. (2021) discussed the integration of molecular diagnostics, imaging, and clinical data to advance precision oncology. They highlighted the challenges and opportunities in developing multimodal biomarkers to propel the field forward. Their research demonstrated the immense potential of integrative approaches in improving the accuracy and efficacy of cancer treatment by combining multiple data types (Boehm et al., 2021).

The core of systems biology approaches lies in understanding the complexity of biological systems through multi-layered data integration. By combining genomics, transcriptomics, proteomics, and metabolomics data, researchers can construct comprehensive biological network models, leading to better predictions of treatment responses. These methods are significant not only in theory but also in practical applications, showing potential for improving patient outcomes through enhanced therapeutic strategies.

4 Evaluation and Validation of Predictive Models

4.1 Criteria for model evaluation

To evaluate predictive models accurately, several metrics are essential. The primary criteria include accuracy, sensitivity, and specificity. Accuracy measures the overall correctness of the model's predictions. Sensitivity (or recall) assesses the model's ability to correctly identify true positives, which is crucial in medical contexts to avoid missing actual cases of disease. Specificity, on the other hand, measures the model's ability to correctly identify true negatives, helping to reduce false positives. Together, these metrics provide a comprehensive evaluation of a model's performance in predicting treatment responses in cancer patients (Sidey-Gibbons and Sidey-Gibbons, 2019).

Moreover, advanced models often employ additional metrics like precision, F1 score, and the area under the receiver operating characteristic curve (AUC-ROC). Precision, the ratio of true positives to the total predicted positives, balances sensitivity by considering false positives. The F1 score, which is the harmonic mean of precision and sensitivity, provides a single metric that balances both concerns, particularly useful in imbalanced datasets. The AUC-ROC offers a comprehensive evaluation by plotting the true positive rate against the false positive rate, highlighting the model's capability to distinguish between classes at various threshold settings (Rahman et al., 2017).

4.2 Validation techniques

Validation techniques are critical for assessing the robustness and generalizability of predictive models. Cross-validation, particularly k-fold cross-validation, is commonly used. It involves partitioning the dataset into k subsets, training the model on k-1 subsets, and validating it on the remaining subset. This process is repeated k times with each subset serving as the validation set once, which helps ensure that every instance in the dataset is used for both training and validation. This technique provides a reliable estimate of the model’s performance on unseen data by reducing overfitting and ensuring the model’s generalizability (Xia et al., 2021).

External validation is another crucial technique, involving testing the model on an entirely independent dataset that was not used during the model's training. This method provides a stringent test of the model’s predictive power and generalizability in real-world scenarios. For example, a study developed and validated a machine learning model for predicting lung metastasis in kidney cancer using a large population-based dataset, which demonstrated high accuracy and applicability. Such robust validation is vital to ensure that the predictive models perform well in diverse clinical settings and populations (Yi et al., 2023).

4.3 Real-World application and limitations

The practical application of predictive models in clinical settings involves several challenges and limitations. One significant challenge is the variability in data quality and completeness. Clinical data often contain missing values, inconsistencies, and noise, which can significantly impact the model's performance. Integrating diverse data sources such as electronic health records (EHR), genomic data, and imaging results requires sophisticated data preprocessing and harmonization techniques.

Another limitation is the interpretability of the model. Clinicians need transparent and interpretable models to trust and effectively use these tools for decision-making. Black box models such as deep learning are often highly accurate. Figure 1 shows the deep learning architecture, which combines convolutional neural networks (CNN) and recurrent neural networks (RNN) to integrate image data at different time points and capture the dynamic changes of tumors. This method not only quantitatively evaluates tumor characteristics, but also monitors tumor changes before and after treatment in a non-invasive manner, with the advantages of low cost and high efficiency. In clinical applications, this AI based imaging biomarker can significantly improve patient treatment management and provide personalized treatment plans.

Moreover, the translation of predictive models from research to practice involves navigating regulatory and ethical considerations. Ensuring patient privacy and data security is paramount, particularly when handling sensitive health data. Ethical considerations around the use of AI in clinical settings include ensuring fairness and avoiding biases that may arise from the training data.The real-world application of these models requires continuous

monitoring and updating. As new data become available and treatment protocols evolve, models need to be retrained and validated to maintain their accuracy and relevance. This ongoing process ensures that predictive models remain effective tools for improving patient outcomes in the dynamic landscape of cancer treatment.

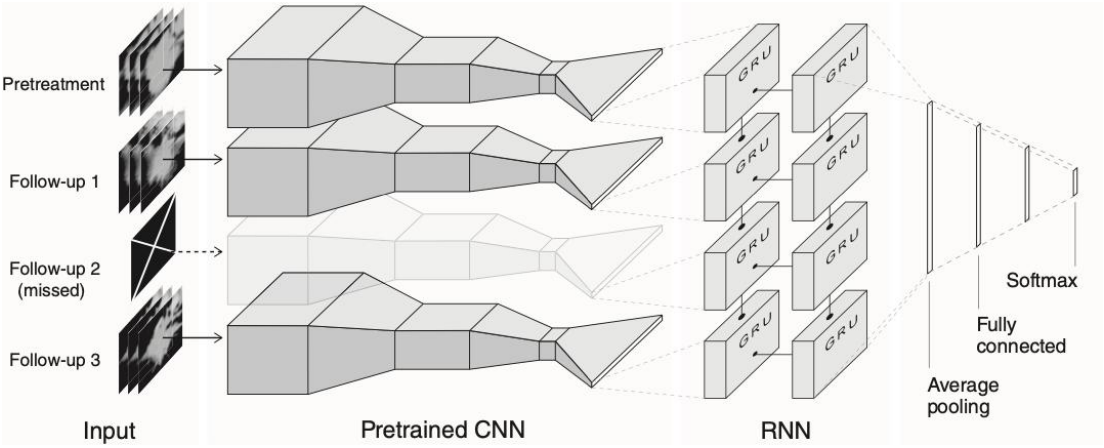

Figure 1 Deep learning architectures (Adopted from Xu et al., 2019)

Image caption: The neural architecture includes ResNet CNNs merged with an RNN, and was trained on baseline and follow-up scans. The input axial slices of 50x50 mm^2 centered on the selected seed point were used as inputs to the model. They were spaced 5 mm apart; the center slice is on the same axial slice as the seed point. Deep learning networks are trained on natural RGB images and thus need three image slices for input. The outputs of each CNN model are input into the RNN, with a GRU for time-varying inputs. Masking was performed on certain inputs of the CNN so that the recurrent network takes missed scans into account. The final softmax layer provides the prediction (Adopted from Xu et al., 2019)

5 Case Studies and Applications

5.1 Breast cancer

In the treatment of breast cancer, circulating tumor DNA (ctDNA) as a non-invasive biomarker to predict the response of neoadjuvant therapy (NST) is receiving more and more attention. The study by Zhou et al. (2022) showed that the detection and persistence of ctDNA can significantly predict the response effect of NST. In a study, they analyzed 93 genes of 193 patients with early breast cancer, designed a patient specific ctDNA tracking detection program, and found that the presence of ctDNA during the mid-term treatment (MT) was significantly related to the higher residual cancer burden (RCB) (Zhou et al., 2022).

The study found that among 145 patients with baseline (BL) plasma samples, 63 (43.4%) detected ctDNA at BL. Among these patients, 25 (39.7%) still detected ctDNA at MT, and 15 (23.8%) still had ctDNA at the end of treatment (EOT). Further analysis showed that out of 31 patients who detected ctDNA during MT, 30 (96.8%) were treatment unresponsive (RCB II and III), and only 1 patient achieved RCB I. In addition, patients without RCB 0 detected ctDNA at MT, only 6.7% of RCB I patients detected ctDNA at MT, while 30.6% and 29.6% of RCB II and III patients detected ctDNA at MT, respectively. From these data, it can be seen that ctDNA detection in the mid-term of NST can serve as a negative marker for predicting tumor response. This means that the persistent presence of ctDNA may indicate ineffective treatment and require adjustment of treatment strategies (Figure 2).

The results of this study underscore the potential of liquid biopsy in the treatment of breast cancer. Compared with traditional imaging methods, liquid biopsy has the advantages of non-invasive and repeatable, especially suitable for frequent monitoring of early breast cancer patients. In terms of clinical application, this study supports the effectiveness of ctDNA as an early response marker, which can help identify patients who may not require breast surgery after NST, thereby reducing unnecessary invasive treatment.

5.2 Lung cancer

In the treatment of non-small cell lung cancer (NSCLC), the integration method combines multiple data types, including imaging data, molecular markers, and clinical data, to improve the prediction accuracy of treatment

response. Through this comprehensive analysis method, researchers can gain a more comprehensive understanding of the biological characteristics and treatment response mechanisms of tumors.

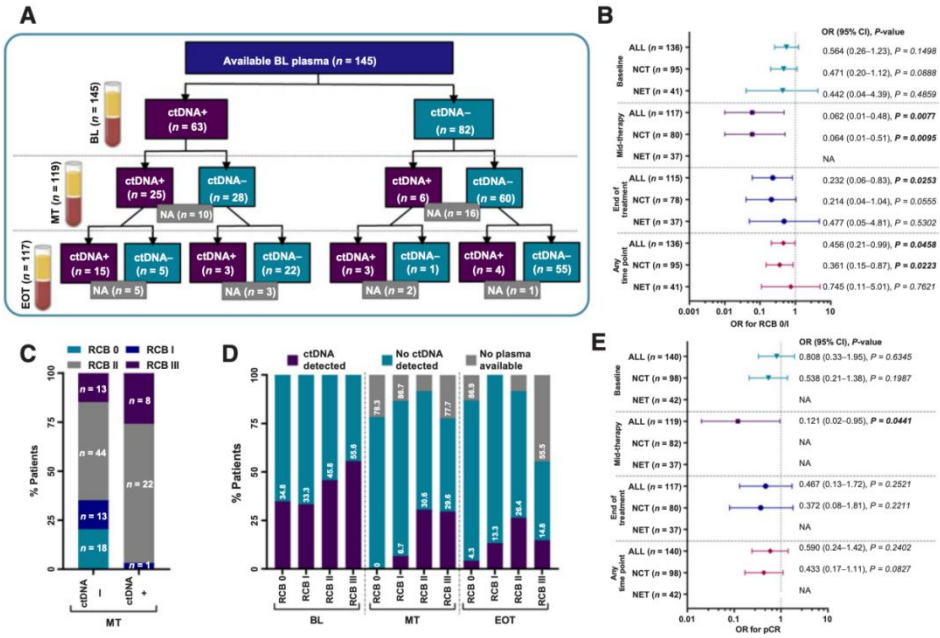

Figure 2 Predictive value of ctDNA (Adopted from Zhou et al., 2022)

Image caption: A, Flow chart depicting patients with (ctDNAþ) and without (ctDNA) detectable ctDNA at BL, MT, and EOT. NA, no plasma available. B, OR with 95% confidence intervals (CI) and P values for ctDNA detection at BL, MT, EOT, or all time points to predict tumor response (RCB 0/I vs. RCB II/III) calculated from univariate logistic regression models. C, Plotted are the fractions of patients stratified by response (RCB 0–III) with (ctDNAþ) and without (ctDNA) detectable ctDNA at MT. D, Detection rates of ctDNA at BL, MT, and EOT stratified by RCB scores (E) same as in B but for pCR. NA, not analyzable (Adopted from Zhou et al., 2022)

The study by Xu et al. (2019) demonstrated the application of deep learning based integration methods in predicting lung cancer treatment response. This study significantly improved the predictive ability of clinical outcomes by analyzing time series CT imaging data. The study used two datasets, dataset A included 179 stage III NSCLC patients who received radiotherapy and chemotherapy, and dataset B included 89 patients who underwent surgery after radiotherapy and chemotherapy. Research has found that as the number of follow-up scan data increases, the predictive performance of the model gradually improves. For example, in predicting the overall 2-year survival rate, the AUC values of the model after each follow-up scan were 0.58 (baseline scan), 0.64 (1-month follow-up), 0.69 (3-month follow-up), and 0.74 (6-month follow-up), respectively, demonstrating the importance of follow-up data in survival prediction (Figure 3) (Xu et al., 2019).

The application of integration methods in the treatment of NSCLC is not limited to the analysis of imaging data, but also involves the comprehensive utilization of molecular markers and clinical data. For example, researchers can combine genomic sequencing data with radiomics characteristics of tumors to further improve the accuracy of predictive models. This multi omics integration analysis enables predictive models to not only recognize the physical characteristics of tumors, but also reveal their molecular mechanisms, providing more comprehensive information for personalized treatment. By combining baseline and follow-up CT imaging data, molecular markers, and clinical data, deep learning models can accurately predict the clinical outcomes of NSCLC patients, providing new tools and methods for personalized healthcare. This not only improves the accuracy and efficiency of image analysis, but also has a profound impact on future clinical practice.

5.3 Colorectal cancer

In the treatment of colorectal cancer (CRC), comprehensive molecular analysis has become an important research method. By integrating genomic, transcriptome, and proteomic data, researchers can gain a more comprehensive understanding of the biological characteristics and treatment response mechanisms of tumors.

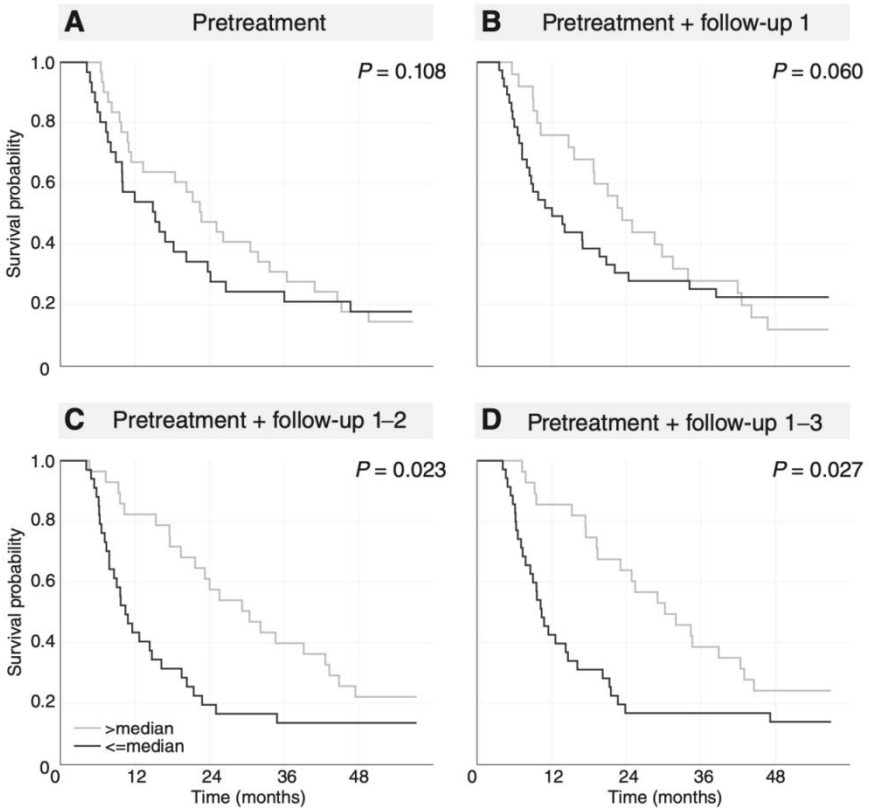

Figure 3 Performance deep learning biomarkers on validation datasets (Adopted from Xu et al., 2019)

Image caption: The deep learning models were evaluated on an independent test set for performance. The 2-year overall survival Kaplan–Meier curves were performed with median stratification (derived from the training set) of the low and high mortality risk groups with no follow-up or up to three follow-ups at 1, 3, and 6 months posttreatment for dataset A (72 definitive patients in the independent test set, log-rank test $P < 0.05$ for > one follow-up) (Adopted from Xu et al., 2019)

Li et al. (2020) conducted genome-wide sequencing, transcriptome sequencing, and proteomic analysis on samples from 146 Chinese colorectal cancer patients, revealing significant differences between primary and metastatic tumors. Research has found that although metastatic tumors have high genetic similarity to primary tumors, there is significant heterogeneity in protein expression patterns. Especially in kinase network analysis, there are significant differences in protein expression patterns between primary tumors and their liver metastases, indicating the role of different signaling pathways in tumor metastasis (Figure 4) (Li et al., 2020) .

In addition, through joint analysis of proteomics and phosphoproteomics, the study successfully classified CRC into three subtypes with different clinical outcomes. The integration of multi omics data enables researchers to identify specific phosphorylation patterns that are closely related to drug responses. This is particularly important for patients without obvious targeted mutations, as these phosphorylation patterns can serve as new therapeutic targets, providing new strategies for personalized treatment.

The results of this study indicate that the combination of genomics and proteomics is of great significance in understanding the complexity of CRC. The application of comprehensive molecular analysis in the treatment of colorectal cancer has demonstrated its enormous potential and value. By integrating multiple data types, researchers can gain a more comprehensive understanding of the biological characteristics of tumors and develop more precise and personalized treatment strategies, thereby improving the prognosis and quality of life of patients.

5.4 Pan-Cancer studies

Integrative Principal Component Regression (iPCR) has been applied successfully in pan-cancer studies to predict drug responses. This method combines various data types, including genomic, transcriptomic, and proteomic data, to create robust predictive models. The integration of these diverse data sources enhances the accuracy of predictions and helps tailor treatments to individual patient profiles(Pender et al., 2020).

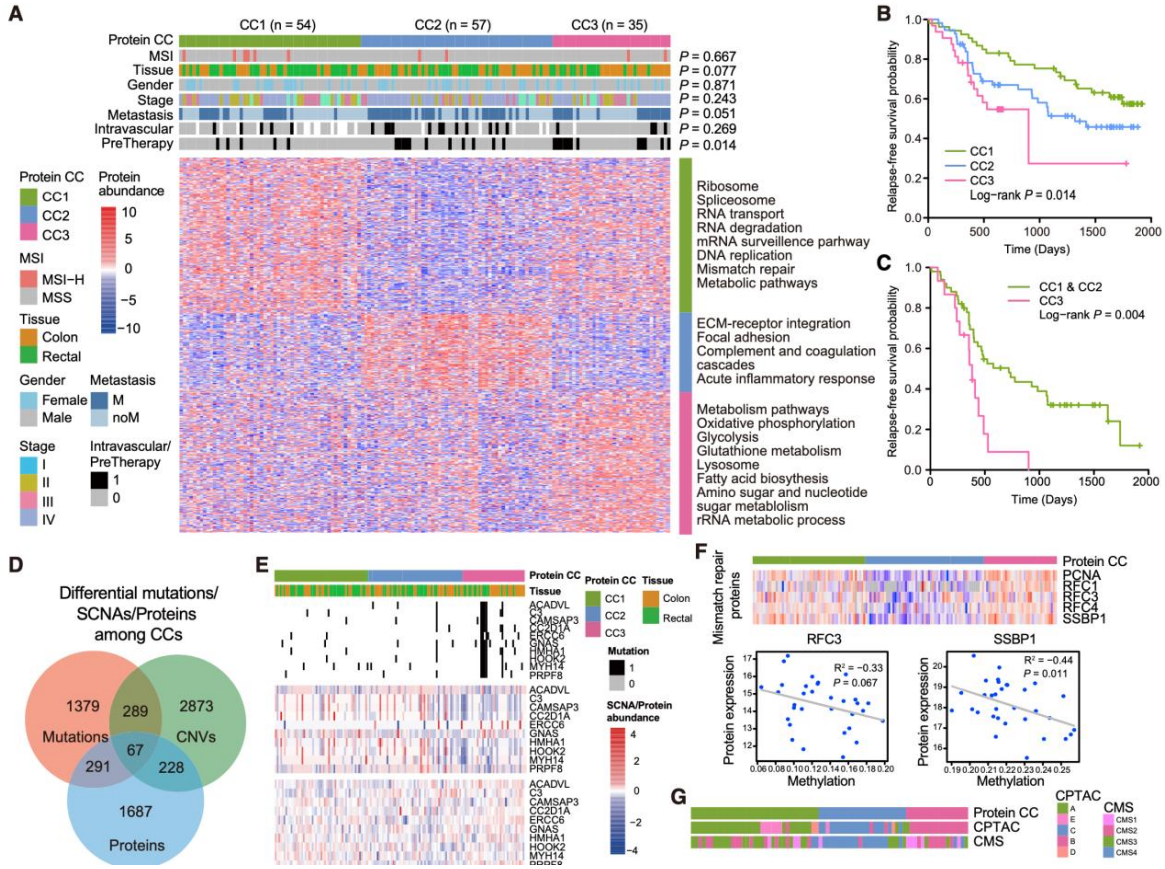

Figure 4 Proteomic subtyping of CCRC and clinical implications for each subtype (Adopted from Li et al., 2020)

Image caption: (A) Consensus clustering based on differentially expressed proteins between tumor and remote normal tissues. Each column represents a patient sample and rows indicate proteins. (B) Kaplan-Meier curves for relapse-free survival based on proteomic subgroups. The p value was calculated by log rank test. (C) Kaplan-Meier curves for relapse-free survival based on proteomic subgroups for mCRC. The p value was calculated by log rank test. (D) Venn diagram illustrates the overlap of differential gene mutations, SCNAs, or proteins among three CCs.(E) The top 10 differentially mutated genes that also showed differences in SCNA and protein levels. (F) The expression of proteins enriched in the mismatch repair pathway (top). The correlation between methylation level and protein expression of RFC3 and SSBP1 (bottom). Correlation coefficients and p values were calculated by the Spearman correlation method. (G) Comparison of proteomic subtyping of non-mCRC with previous subtyping results based on RNA (Guinney et al., 2015) or Western CRC patients (Vasaikar et al., 2019; Zhang et al., 2014). M, mCRC; noM, non-mCRC (Adopted from Li et al., 2020)

Pan-cancer studies that utilize integrative approaches have demonstrated high predictive accuracy across multiple cancer types. These studies highlight the potential for broad applications of integrative models in clinical practice, providing valuable insights for personalized cancer treatment strategies.

6 Challenges and Limitations

6.1 Data heterogeneity

The heterogeneous nature of cancer poses significant challenges to predicting treatment responses. Tumor heterogeneity involves variations at the genetic, cellular, and microenvironmental levels, leading to diverse responses to therapies. Majumder et al. (2015) highlighted the complexity of capturing tumor heterogeneity in personalized treatment strategies. Their study utilized engineered tumor ecosystems to maintain heterogeneity and used this data to predict clinical responses to anticancer drugs, emphasizing the need for models that can accurately reflect the diverse tumor environments (Majumder et al., 2015).

Standardizing data across different platforms and studies remains a significant barrier. Data collected from various sources, such as genomic sequencing, proteomics, and imaging, often lack consistency in format and quality. This inconsistency can lead to challenges in integrating and interpreting the data effectively. Mathur et al. (2020)

discussed the importance of standardizing data to optimize treatment strategies and delay resistance evolution. They proposed a population dynamics model incorporating both pre-existing and acquired resistance, demonstrating the need for standardized, high-quality data for accurate predictions (Mathur et al., 2020). Figure 5 illustrates the importance of tumor matrix protein (TMP) in preserving primary tumor features. The diversity of data types and sources was fully reflected in this study, and the graph shows different types of experimental data, including protein abundance, cell proliferation, tumor area, and morphological changes. These data come from various sources, such as scanning electron microscopy (SEM) images, immunofluorescence (IF) staining, hematoxylin eosin (H&E) staining, and Ki-67 staining.

6.2 Technical and computational challenges

Analyzing high-dimensional data is a critical challenge in precision oncology. The vast amount of data generated from high-throughput sequencing and other omics technologies requires sophisticated computational tools for effective analysis. Fan et al. (2020) highlighted the computational challenges associated with single-cell transcriptomics, which provides detailed insights into tumor heterogeneity. Their review emphasized the need for advanced algorithms to handle the complexity of high-dimensional data, including trajectory and RNA velocity analysis to delineate tumoral evolution (Fan et al., 2020).

The computational resources required for analyzing large-scale datasets are substantial. Deep learning and other advanced machine learning techniques necessitate high computational power and memory. Sakellaropoulos et al. (2019) demonstrated that deep neural networks outperformed traditional machine learning frameworks in predicting drug responses, but also noted the significant computational demands of these methods. Efficient use of computational resources is essential for developing scalable models that can be applied in clinical settings (Sakellaropoulos et al., 2019).

6.3 Ethical and privacy concerns

Ensuring the privacy and security of patient data is paramount in cancer research. The integration of diverse datasets, including genomic, clinical, and imaging data, increases the risk of breaches in patient confidentiality. Researchers must implement stringent data protection protocols to safeguard patient information. Levitin et al. (2018) discussed the ethical considerations in single-cell transcriptomic analysis, highlighting the importance of maintaining patient privacy while leveraging detailed molecular data for treatment predictions (Levitin et al., 2018).

Ethical considerations extend beyond privacy to include issues of consent and data ownership. Patients must be fully informed about how their data will be used and the potential implications of data integration. Ensuring ethical standards in data handling and usage is critical to maintaining public trust and advancing precision oncology. Berlow et al. (2018) emphasized the ethical dimensions of integrating patient-derived data in personalized treatment models, advocating for transparent and ethical research practices to enhance the applicability of computational predictions (Berlow et al., 2018).

7 Future Directions

7.1 Advancements in technology

Emerging technologies in molecular profiling and imaging are driving advancements in predicting treatment responses for cancer. Tools like high-throughput sequencing and RNA sequencing have greatly improved the ability to detect predictive and prognostic molecular alterations in tumors. Gambardella et al. (2020) highlighted that these advancements enable precision medicine by identifying specific molecular changes in cancer cells, which guide personalized treatment strategies (Gambardella et al., 2020).

Advances in computational power and algorithms are crucial for managing large-scale biological data. Deep learning and other AI technologies require substantial computational resources for complex data analysis. Sakellaropoulos et al. (2019) demonstrated the superiority of deep neural networks in predicting drug responses, although these methods demand significant computational power. These improvements are essential for developing scalable models applicable in clinical settings (Sakellaropoulos et al., 2019).

7.2 Collaborative research and data sharing

Collaborative research across multiple institutions is vital for advancing cancer research and treatment prediction. Such collaborations can integrate diverse data sources, enhancing the comprehensiveness and applicability of studies. Sicklick et al. (2019) demonstrated the feasibility of personalized combination therapies in the I-PREDICT study, a cross-institutional prospective study that used tumor DNA sequencing to provide timely treatment recommendations, significantly improving disease control rates and patient survival (Sicklick et al., 2019).

Data sharing and open science initiatives are crucial for fostering advancements in cancer research. By sharing large-scale biological data, researchers can gain a more comprehensive understanding of cancer's molecular mechanisms and develop more effective treatment strategies. These platforms not only increase research transparency but also facilitate innovative discoveries and methodologies.

7.3 Personalized medicine and beyond

The future of personalized medicine lies in integrating various data types to create precise treatment strategies. Ahmed et al. (2022) introduced an enhanced deep learning model that integrates gene expression data, mutation profiles, and drug response data, significantly improving the accuracy of drug response predictions and demonstrating the potential of personalized treatment approaches (Ahmed et al., 2022).

The widespread adoption of personalized medicine approaches can greatly improve clinical practice and patient care. By tailoring treatment plans to individual patient characteristics, clinicians can enhance treatment efficacy and reduce adverse effects. Doudican et al. (2015) illustrated the practical application of personalized cancer treatment through a predictive simulation approach, combining patient-specific genetic mutations and copy number variations to devise effective drug combinations for high-risk multiple myeloma patients (Doudican et al., 2015).

8 Concluding Remarks

This review highlights several integrative approaches for predicting treatment responses in advanced solid tumors. Key insights include the effectiveness of combining molecular, imaging, and clinical data to enhance predictive accuracy. The adoption of advanced computational models, including machine learning and AI, has shown significant promise in refining prediction capabilities. These integrative approaches have demonstrated the potential to improve personalized treatment strategies and patient outcomes by providing a more comprehensive understanding of tumor biology and treatment responses.

Integrative approaches have significant implications for both research and clinical practice. For researchers, these methods offer a holistic view of cancer, facilitating the development of more accurate and personalized predictive models. Clinically, integrative approaches enable the creation of tailored treatment plans that can improve efficacy and reduce adverse effects. By leveraging diverse data sources, clinicians can make more informed decisions, ultimately enhancing patient care and outcomes.

The future of integrative approaches in predicting treatment responses for advanced solid tumors is promising. Continued advancements in molecular profiling, imaging technologies, and computational algorithms are expected to further enhance the precision and applicability of predictive models. Collaborative research and data sharing initiatives will be crucial in expanding the available datasets for model training and validation, improving the robustness and generalizability of these models. The integration of personalized medicine approaches is likely to transform clinical practice, enabling more effective and individualized patient care. These developments herald a new era of precision oncology, where treatment decisions are increasingly driven by comprehensive, integrative data analyses.

Acknowledgments

Sincerely thank the peer reviewers for their valuable feedback and suggestions on my study.

Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Ahmed H., Hamad S., Shedeed H., and Hussein A., 2022, Enhanced deep learning model for personalized cancer treatment, IEEE Access, 10: 106050-106058.
https://doi.org/10.1109/ACCESS.2022.3209285

Berlow N., Rikhi R., Geltzeiler M., Abraham J., Svalina M., Davis L., Wise E., Mancini M., Noujaim J., Mansoor A., Quist M., Matlock K., Goros M., Hernandez B., Doung Y., Thway K., Tsukahara T., Nishio J., Huang E., Airhart S., Bult C., Gandour-Edwards R., Maki R., Jones R., Michalek J., Milovancev M., Ghosh S., Pal R., and Keller C., 2018, Probabilistic modeling of personalized drug combinations from integrated chemical screen and molecular data in sarcoma, BMC Cancer, 19: 593.
https://doi.org/10.1186/s12885-019-5681-6

Boehm K., Khosravi P., Vanguri R., Gao J., and Shah S., 2021, Harnessing multimodal data integration to advance precision oncology, Nature Reviews Cancer, 22: 114-126.
https://doi.org/10.1038/s41568-021-00408-3

Bulen B., Khazanov N., Lamb L., Hovelson D., Kwiatkowski K., Johnson D., Rhodes D., and Tomlins S., 2023, Validation of an integrative pan-solid tumor predictor of pembrolizumab monotherapy benefit, Cancer Research, 83(7): 43-48.
https://doi.org/10.1158/1538-7445.am2023-4348

Chung W., Chen S., Ko T., Lin Y., Lin S., Lo Y., Tseng S., and Yu C., 2022, An integrative clinical model for the prediction of pathological complete response in patients with operable stage II and stage III triple-negative breast cancer receiving neoadjuvant chemotherapy, Cancers, 14(17): 4170.
https://doi.org/10.3390/cancers14174170

Davis A., Iams W., Chan D., Oh M., Lentz R., Peterman N., Robertson A., Shah A., Srivas R., Wilson T., Lambert N., George P., Wong B., Wood H., Close J., Tezcan A., Nesmith K., Tezcan H., and Chae Y., 2019, Early assessment of molecular progression and response by whole-genome circulating tumor DNA in advanced solid tumors, Molecular Cancer Therapeutics, 19: 1486-1496.
https://doi.org/10.1158/1535-7163.MCT-19-1060

Doudican N., Kumar A., Singh N., Nair P., Lala D., Basu K., Talawdekar A., Sultana Z., Tiwari K., Tyagi A., Abbasi T., Vali S., Vij R., Fiala M., King J., Perle M., and Mazumder A., 2015, Personalization of cancer treatment using predictive simulation, Journal of Translational Medicine, 13: 43.
https://doi.org/10.1186/s12967-015-0399-y

Fan J., Slowikowski K., and Zhang F., 2020, Single-cell transcriptomics in cancer: computational challenges and opportunities, Experimental & Molecular Medicine, 52: 1452-1465.
https://doi.org/10.1038/s12276-020-0422-0

Gambardella V., Tarazona N., Cejalvo J., Lombardi P., Huerta M., Roselló S., Fleitas T., Roda D., and Cervantes A., 2020, Personalized medicine: recent progress in cancer therapy, Cancers, 12(4): 1009.
https://doi.org/10.3390/cancers12041009

Halasz M., Kholodenko B., Kolch W., and Santra T., 2016, Integrating network reconstruction with mechanistic modeling to predict cancer therapies, Science Signaling, 9: ra114-ra114.
https://doi.org/10.1126/scisignal.aae0535

Levitin H., Yuan J., and Sims P., 2018, Single-Cell transcriptomic analysis of tumor heterogeneity, Trends in Cancer, 4(4): 264-268.
https://doi.org/10.1016/j.trecan.2018.02.003

Li C., Sun Y.D., Yu G.Y., Cui J.R., Lou Z., Zhang H., Huang Y., Bai C.G., Deng L.L., Liu P., Zheng K., Wang Y.H., Wang Q.Q., Li Q.R., Wu Q.Q., Liu Q., Shyr Y., Li Y.X., Chen L.N., Wu J.R., Zhang W., and Zeng R., 2020, Integrated omics of metastatic colorectal cancer, Cancer Cell, 38(5): 734-747.
https://doi.org/10.1016/j.ccell.2020.08.002

Liu Q., Li G., and Baladandayuthapani V., 2023, Pan-Cancer drug response prediction using integrative principal component regression, bioRxiv, 10(5): 560366.
https://doi.org/10.1101/2023.10.03.560366

Majumder B., Baraneedharan U., Thiyagarajan S., Radhakrishnan P., Narasimhan H., Dhandapani M., Brijwani N., Pinto D., Prasath A., Shanthappa B., Thayakumar A., Surendran R., Babu G., Shenoy A., Kuriakose M., Bergthold G., Horowitz P., Loda M., Beroukhim R., Agarwal S., Sengupta S., Sundaram M., and Majumder P., 2015, Predicting clinical response to anticancer drugs using an ex vivo platform that captures tumour heterogeneity, Nature Communications, 6: 6169.
https://doi.org/10.1038/ncomms7169

Mathur D., Taylor B., Chatila W., Schultz N., Razavi P., and Xavier J., 2020, Abstract PO-114: mathematical modeling of tumor heterogeneity to optimize treatment scheduling and delay the evolution of resistance, Cancer Research, 80(21): PO-114.
https://doi.org/10.1158/1538-7445.tumhet2020-po-114

Pender A., Titmuss E., Pleasance E., Fan K., Pearson H., Brown S., Grisdale C., Topham J., Shen Y., Bonakdar M., Taylor G., Williamson L., Mungall K., Chuah E., Mungall A., Moore R., Lavoie J., Yip S., Lim H., Renouf D., Sun S., Holt R., Jones S., Marra M., and Laskin J., 2020, Genome and transcriptome biomarkers of response to immune checkpoint inhibitors in advanced solid tumors, Clinical Cancer Research, 27(1): 202-212.
https://doi.org/10.1158/1078-0432.CCR-20-1163

Rahman M., Ambler G., Choodari-Oskooei B., and Omar R., 2017, Review and evaluation of performance measures for survival prediction models in external validation settings, BMC Medical Research Methodology, 17: 60.
https://doi.org/10.1186/s12874-017-0336-2

Rodin A., Uduman M., Lee P., Marincola F., and Branciamore S., 2022, Editorial: systems biology methods in computational immuno-oncology, Frontiers in Genetics, 13:885252.
https://doi.org/10.3389/fgene.2022.885252

Sailer V., Eng K., Zhang T., Bareja R., Pisapia D., Sigaras A., Bhinder B., Romanel A., Wilkes D., Sticca E., Cyrta J., Rao R., Sahota S., Pauli C., Beg S., Motanagh S., Kossai M., Fontunge J., Puca L., Rennert H., Xiang J., Greco N., Kim R., Macdonald T., McNary T., Blattner-Johnson M., Schiffman M., Faltas B., Greenfield J., Rickman D., Andreopoulou E., Holcomb K., Vahdat L., Scherr D., Besien K., Barbieri C., Robinson B., Fine H., Ocean A., Molina A., Shah M., Nanus D., Pan Q., Demichelis F., Tagawa S., Song W., Mosquera J., Sboner A., Rubin M., Elemento O., and Beltran H., 2019, Integrative molecular analysis of patients with advanced and metastatic cancer, JCO Precision Oncology, 3: 1-12.
https://doi.org/10.1200/po.19.00047

Sakellaropoulos T., Vougas K., Narang S., Koinis F., Kotsinas A., Polyzos A., Moss T., Piha-Paul S., Zhou H., Kardala E., Damianidou E., Alexopoulos L., Aifantis I., Townsend P., Panayiotidis M., Sfikakis P., Bartek J., Fitzgerald R., Thanos D., Shaw K., Petty R., Tsirigos A., and Gorgoulis V., 2019, A deep learning framework for predicting response to therapy in cancer, Cell Reports, 29(11): 3367-3373.
https://doi.org/10.1016/j.celrep.2019.11.017

Sicklick J., Kato S., Okamura R., Schwaederlé M., Hahn M., Williams C., De P., Krie A., Piccioni D., Miller V., Ross J., Ross J., Benson A., Webster J., Stephens P., Lee J., Fanta P., Lippman S., Leyland-Jones B., and Kurzrock R., 2019, Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study, Nature Medicine, 25: 744-750.
https://doi.org/10.1038/s41591-019-0407-5

Sidey-Gibbons J., and Sidey-Gibbons C., 2019, Machine learning in medicine: a practical introduction, BMC Medical Research Methodology, 19: 64.
https://doi.org/10.1186/s12874-019-0681-4

Silberberg G., Walling B., Wesa A., Audia A., Sloma I., Zeng Y., Han G., Tang J., Pammer P., Bakayoko A., Ciznadija D., Vishwakarma B., Mosesson Y., Zipeto M., and Ritchie M., 2022, Pharmaco-Pheno-Multiomic integration reveals biomarker profiles and therapeutic response prediction models in leukemia and ovarian cancer, bioRxiv, 7(1): 86-105.
https://doi.org/10.1101/2022.06.14.495846

Sun R., Limkin E., Vakalopoulou M., Dercle L., Champiat S., Han S., Verlingue L., Brandao D., Lancia A., Ammari S., Hollebecque A., Scoazec J., Marabelle A., Massard C., Soria J., Robert C., Paragios N., Deutsch E., and Ferté C., 2018, A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study, The Lancet, Oncology, 19(9): 1180-1191.
https://doi.org/10.1016/S1470-2045(18)30413-3

Uzilov A., Ding W., Fink M., Antipin Y., Brohl A., Davis C., Lau C., Pandya C., Shah H., Kasai Y., Powell J., Micchelli M., Castellanos R., Zhang Z., Linderman M., Kinoshita Y., Zweig M., Raustad K., Cheung K., Castillo D., Wooten M., Bourzgui I., Newman L., Deikus G., Mathew B., Zhu J., Glicksberg B., Moe A., Liao J., Edelmann L., Dudley J., Maki R., Kasarskis A., Holcombe R., Mahajan M., Hao K., Reva B., Longtine J., Starcevic D., Sebra R., Donovan M., Li S., Schadt E., and Chen R., 2016, Development and clinical application of an integrative genomic approach to personalized cancer therapy, Genome Medicine, 8: 62.
https://doi.org/10.1186/s13073-016-0313-0

Wheeler D., Takebe N., Hinoue T., Hoadley K., Cardenas M., Hamilton A., Laird P., Wang L., Johnson A., Dewal N., Miller V., Piñeyro D., Moura M., Esteller M., Shen H., Zenklusen J., Tarnuzzer R., McShane L., Tricoli J., Williams P., Lubensky I., O'Sullivan-Coyne G., Kohn E., Little R., White J., Malik S., Harris L., Weil C., Chen A., Karlovich C., Rodgers B., Shankar L., Jacobs P., Nolan T., Hu J., Muzny D., Doddapaneni H., Korchina V., Gastier-Foster J., Bowen J., Leraas K., Edmondson E., Doroshow J., Conley B., Ivy S., and Staudt L., 2020, Molecular features of cancers exhibiting exceptional responses to treatment, Cancer Cell, 39(1): 38-53.
https://doi.org/10.1016/j.ccell.2020.10.015

Xia F., Allen J., Balaprakash P., Brettin T., Garcia-Cardona C., Clyde A., Cohn J., Doroshow J., Duan X., Dubinkina V., Evrard Y., Fan Y., Gans J., He S., Lu P., Maslov S., Partin A., Shukla M., Stahlberg E., Wozniak J., Yoo H., Zaki G., Zhu Y., and Stevens R., 2021, A cross-study analysis of drug response prediction in cancer cell lines, Briefings in Bioinformatics, 23(1): bbab356.
https://doi.org/10.1093/bib/bbab356

Xu Y., Hosny A., Zeleznik R., Parmar C., Coroller T., Franco I., Mak R., and Aerts H., 2019, Deep learning predicts lung cancer treatment response from serial medical imaging, Clinical Cancer Research, 25(11): 3266-3275.
https://doi.org/10.1158/1078-0432.CCR-18-2495

Yi X., Zhang Y., Cai J., Hu Y., Wen K., Xie P., Yin N., Zhou X., and Luo H., 2023, Development and external validation of machine learning-based models for predicting lung metastasis in kidney cancer: a large population-based study, International Journal of Clinical Practice, 2023(1): 1-13.
https://doi.org/10.1155/2023/8001899

Zhou Q., Gampenrieder S.P., Frantal S., Rinnerthaler G., Singer C.F., Egle D., Pfeiler G., Bartsch R., Wette V., Pichler A., Petru E., Dubsky P.C., Bago-Horvath Z., Fesl C., Rudas M., Ståhlberg A., Graf R., Weber S., Dandachi N., Filipits M., Gnant M., Balic M., and Heitzer E., 2022, Persistence of ctDNA in patients with breast cancer during neoadjuvant treatment is a significant predictor of poor tumor response, Clin Cancer Res, 28(4): 697-707.
https://doi.org/10.1158/1078-0432.CCR-21-3231