Drug Repositioning And Response Detection Based On Randomized Control Trials For Cancer Treatment – A Review

Aman Chandrakar [1], Chetan Kumar Sonkar [1]

Abstract

Drug repositioning is vital in cancer treatment, offering a swift alternative to identify existing drugs repurposable for cancer treatment, bypassing the lengthy and costly traditional drug development process. This approach not only saves resources for the pharmaceutical sector and healthcare systems but also accelerates the discovery of new drugs. Overcoming challenges like data integration and patient classification is crucial in drug repositioning, where methodological advancements utilizing randomized control trials (RCTs) become essential. RCTs provide a systematic way to assess medication efficacy in diverse cancer subpopulations, enhancing the credibility of drug repositioning outcomes. The current study integrates RCTs with advanced data analytics and machine learning to establish a Bayesian Network response detection based on randomized control (BNRD-RC). This approach allows researchers to identify promising drug candidates, predict patient responses, and optimize treatment plans by analyzing diverse datasets, including genomes, proteomics, and clinical records. Beyond personalized treatment, drug repositioning explores medication synergy and combination therapy for rare cancer types. Simulation analysis significantly aids in validating the efficacy and safety of repositioned drugs. Through simulations of clinical scenarios and treatment outcomes, researchers can assess the impact of drug repositioning on patient survival, quality of life, and healthcare costs.

Keywords: Drug Repositioning, Response Detection, Randomized Control, Cancer Treatment

Significance | The cancer treatment will be accelerated through drug repositioning.

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1. Introduction

Drug repositioning and response detection in cancer treatment pose significant challenges during randomized controlled trials (RCTs) (Hernández-Lemus, 2021). While RCTs are the gold standard for assessing drug efficacy, applying them to drug repositioning encounters various issues (Orecchioni, 2019). The complexity and diversity of cancer make it difficult to generalize RCT outcomes to all patient populations (Zhou, 2020). Accurate patient stratification becomes challenging due to potential differences in mechanisms of action for repositioned medications in cancer compared to their original indications. Retrospective studies with small sample sizes may lack statistical power and fail to represent the spectrum of cancer cases (Nowak-Sliwinska, 2019).

RCTs are susceptible to bias and confounding, leading to potentially misleading inferences (Begley, 2021). Regulatory requirements for substantial clinical trial data in repositioning medication approvals pose ethical dilemmas when routine therapy is withheld (Pushpakom, 2019). The dynamic nature of cancer over time is not fully captured by RCTs (Reay, 2021). To address

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these challenges, researchers explore real-world data, biomarker-driven trials, and adaptable study designs that account for new medications and evolving cancer landscapes (Mousavi, 2020).

While RCTs remain crucial, addressing the variability of the disease, complexities in patient selection, and limitations of retrospective research in drug repositioning for cancer demands innovative approaches (Shukla, 2021). In light of RCT findings, several methods have emerged for drug repositioning and response detection in cancer treatment:

Standard randomized controlled trials (RCTs) involve dividing patients into two groups: one receiving the regular medication and the other the repositioned drug (Tanoli, 2021). The comparison of effectiveness and safety results between these groups informs the study. However, traditional RCTs face challenges related to patient selection, ethical concerns, and limited sample sizes (Kingsmore, 2020).

Adaptive RCTs offer flexibility by allowing researchers to alter the trial's design, adjusting the proportion of patients in each treatment arm or eliminating ineffective arms (Cheng, 2019). Successful implementation requires careful planning and management, optimizing resource allocation and integrating emerging data trends (Zhang, 2020).

Basket trials include patients with diverse cancer histologies but a common genetic mutation, while umbrella trials focus on a single histology with varied genetic profiles (Yang, 2022). These trials address cancer heterogeneity by guiding personalized treatment based on genetic markers, enhancing the precision of medicine selection (Jin, 2012).

Biomarker-driven trials predict patient responses to repositioned medications using biomarkers. Stratifying patients based on these indicators improves the chances of identifying clinically relevant treatment responses (Vivarelli, 2020).

In drug repositioning and response detection for cancer treatment using RCTs, stringent patient selection criteria are essential due to potential differences in mechanisms of action for repositioned pharmaceuticals (Lee, 2016). Ethical concerns arise when patients are denied regular medications for experimental repositioning drugs. Small sample sizes and patient heterogeneity may reduce the statistical power of RCTs, and capturing long-term therapy effects is challenging due to the evolving nature of cancer and its genetics (Nagaraj, 2018). Despite being necessary, RCTs for repositioned medications can be costly and time-consuming due to regulatory requirements for substantial data. Nevertheless, they remain crucial for advancing medication repositioning in cancer treatment (Cheng, 2017).

Our review aims to streamline cancer drug repositioning, a strategy repurposing existing drugs for cancer treatment, expediting drug development and saving time and resources. Using randomized controlled trials (RCTs), advanced analytics, and machine learning, we establish a robust Bayesian Network response detection approach (BNRD-RC). This method identifies potential drug candidates, predicts patient reactions, and optimizes treatment regimens, enhancing drug repositioning's credibility and efficiency. The research also explores broader applications, investigating drug synergy and combination treatments for rare cancers. Simulation analysis verifies the efficacy and safety of repositioned medications, assessing their impact on patient survival, quality of life, and healthcare expenditures.

The paper discusses existing techniques for RCTs in cancer treatment (Ioakeim-Skoufa, 2023). Section 3 introduces a new method for detecting responses in Bayesian networks, termed Bayesian Network response detection with randomized controls (BNRD-RC). Section 4 analyzes the results, and Section 5 concludes based on the analysis. The comprehensive approach focuses on identifying repositioned drugs, optimizing their usage, and examining their consequences in cancer care, marking a significant advancement in drug repositioning.

2. Literature Review

This review provides a comprehensive insight on the potential of repurposing medications developed for Type 2 Diabetes Mellitus (T2DM) to treat other diseases, such as cancer, neurological disorders, and cardiovascular diseases (Ferrari & Lüscher,2016). The use of computational technology, particularly machine learning approaches, has accelerated the process of drug repositioning (Ashburn et al,2004). The article highlights the success stories of drug repositioning based on knowledge and molecular characterization of diseases. It also addresses the disappointing clinical outcomes of treatment approaches targeting the tumor microenvironment (TME) and explores the potential of combination therapies.

The development of measures like structural topological networks (STN) assists in identifying connections between drugs and diseases, facilitating drug repositioning efforts (Pushpakom et al,2019). The challenges in treating glioblastoma (GBM) are discussed, emphasizing the potential of repurposed drugs due to their simplicity in clinical transfer (Ekins et al, 2016).The suggested method, Bayesian Network response detection based on randomized control (BNRD-RC), is highlighted as a promising approach for drug repositioning and response detection, particularly in the context of T2DM and its potential repurposing for other medical disorders (Karimi et al, 2019).

The scientists and medical practitioners have enormous interest in repurposing medications developed for Type 2 Diabetes Mellitus (T2DM) for other diseases, such as cancer, neurological disorders, and cardiovascular diseases, has grown. Zhu, S., et al. (2022) developed drugs for T2DM, sparking extensive research into their

potential repurposing. Recent advancements in computational technology, particularly machine learning, have accelerated the drug repositioning process.

Knowledge-based success stories (K-SS), as proposed by Scherman, D. et al. (2020), exemplify how medicines have been repurposed beyond their initial intent, often based on molecular characterizations of the respective diseases. Chance discoveries and purposeful molecular characterizations have contributed to successful repositioning.

Jin, M. Z. et al. (2020) suggested the tumor microenvironment (TME) as a target, but clinical success has been limited. Medications with anticancer activity are being explored for combination therapy, and the article discusses the potential future applications of TME theory.

Structural Topological Networks (STN), developed by Badkas et al. (2021), have helped uncover previously unknown connections between drugs and diseases, aiding in drug repositioning efforts. The article emphasizes the need for broader application efforts, particularly in drug repositioning.

Lyne, S. B. et al. (2021) established treatments for glioblastoma (GBM), but challenges like high costs and failure rates hinder further development. Repurposed drugs show promise for evaluation in patients, with different classes of drugs demonstrating effectiveness against preclinical GBM models.

The proposed Bayesian Network Response Detection based on Randomized Control (BNRD-RC) method emerges as a viable approach for drug repositioning and response detection. This systematic and powerful framework is especially relevant in the context of T2DM and its potential repurposing for other medical disorders (Korotcov et al. 2017).

3. A novel approach to drug positioning

Randomized controlled trials (RCTs) are crucial tools in the proposed approach for drug repositioning and response monitoring in cancer chemotherapy, aiming to identify innovative treatments and enhance patient well-being (DiMasi, et al,2016). The process involves creating an archive of RCTs related to cancer therapies, covering a broad spectrum of medical treatments. Subsequently, powerful machine learning and data mining techniques analyze trial findings to identify potential medications with yet-to-be-established anticancer qualities (Jardim et al,2016). Patient-specific information, including genetic profiles, diagnostic criteria, and treatment results, is utilized for medication efficacy assessment. Patients are categorized based on their vulnerability to drugs using algorithm predictions, paving the way for the development of more personalized treatments (Ribeiro et al,2018). This process leverages prior RCT results and individual patient therapy to expedite drug repositioning and enhance cancer therapy.

Pharmacological and surgical sterilization have been successful treatments for malignancies spreading beyond the initial site, while androgen-absence treatment (ADT) is an option for larger and resistant tumors (Fizazi et al, 2012). Castration-resistant prostate cancer (CRPCA) occurs when cancer cells continue aggressive growth despite ADT (Gravis et al,2013). Figure 1 illustrates current prostate cancer therapies, emphasizing that hormonal therapy is not curative but may be effective. Anti-androgen-driven hormonal control is initially applied for metastatic malignancy, but resistance is a concern (Glass et al,2003). The efficacy of hormonal therapy in reducing tumor size and preventing growth remains uncertain, impacting recipients' lifespan and quality of life. Understanding the mechanisms of chemotherapy resistance is crucial to protect individuals from adverse consequences and identify those not benefiting from therapy. When cancer tissue develops resistance to medication, seeking new treatment strategies becomes essential. CRPCA tolerance mechanisms, such as amplified allergic reactions (Fizazi et al, 2012), AR genetic changes, synergistic stimulants, testosterone-independent AR triggering, and progesterone synthesis, are illustrated in Figure 1. The low solubility of certain cancer drugs in water poses risks of toxicity, formation, and immunity. Chemo ineffectiveness often results from multiple drug resistance, and non-selective anticancer drugs can lead to significant adverse reactions (Loblaw et al,2010). Prostaglandins (PGs) and thromboxanes (TxAs) rely on the presence of amino acid (AA) at this stage. Enzymes like luminal and cytoplasmic A2 are activated by signals within the cellular environment, breaking down amino acids into free AAs (Fig. 2). The oxidation process by cyclooxygenases (COXs) produces prostaglandin G2 when AA release activates COX processes. Subsequently, oxidase transforms it into hydrogen (PGH2) (Fig. 2a), acting as a substrate for cell enzymes to produce active PG substances like prostaglandin D2, prostaglandin E2, prostaglandin F2, prostacyclin I2, and thromboxane A2 (Li et al,2018). Previous evidence highlights the role of chemicals from cyclooxygenase-2 (COX-2) in allergic and painful responses, enhancing local circulation, vessel permeability, cell infiltration, and heat during the AA cascade (Banno et al,2015). Conversely, proteinases from cyclooxygenase-1 (COX-1) play vital roles in maintaining the normal operation of the gastrointestinal mucosa barrier, urinary bladder, and neutrophils. According to kern et al (2002) The accidental inhibition of COX-1 during prolonged NSAIDs medication, leading to a significant drop in gastroprotective PGs, results in serious health complications, causing approximately 15.3 deaths per 100,000 individuals in Europe (Simon et al,1999). These concerns drive scientists to seek novel strategies to address and prevent disorders caused by COX activation. Inhibiting stimulated COX is considered effective as it hinders the synthesis of inflammation-

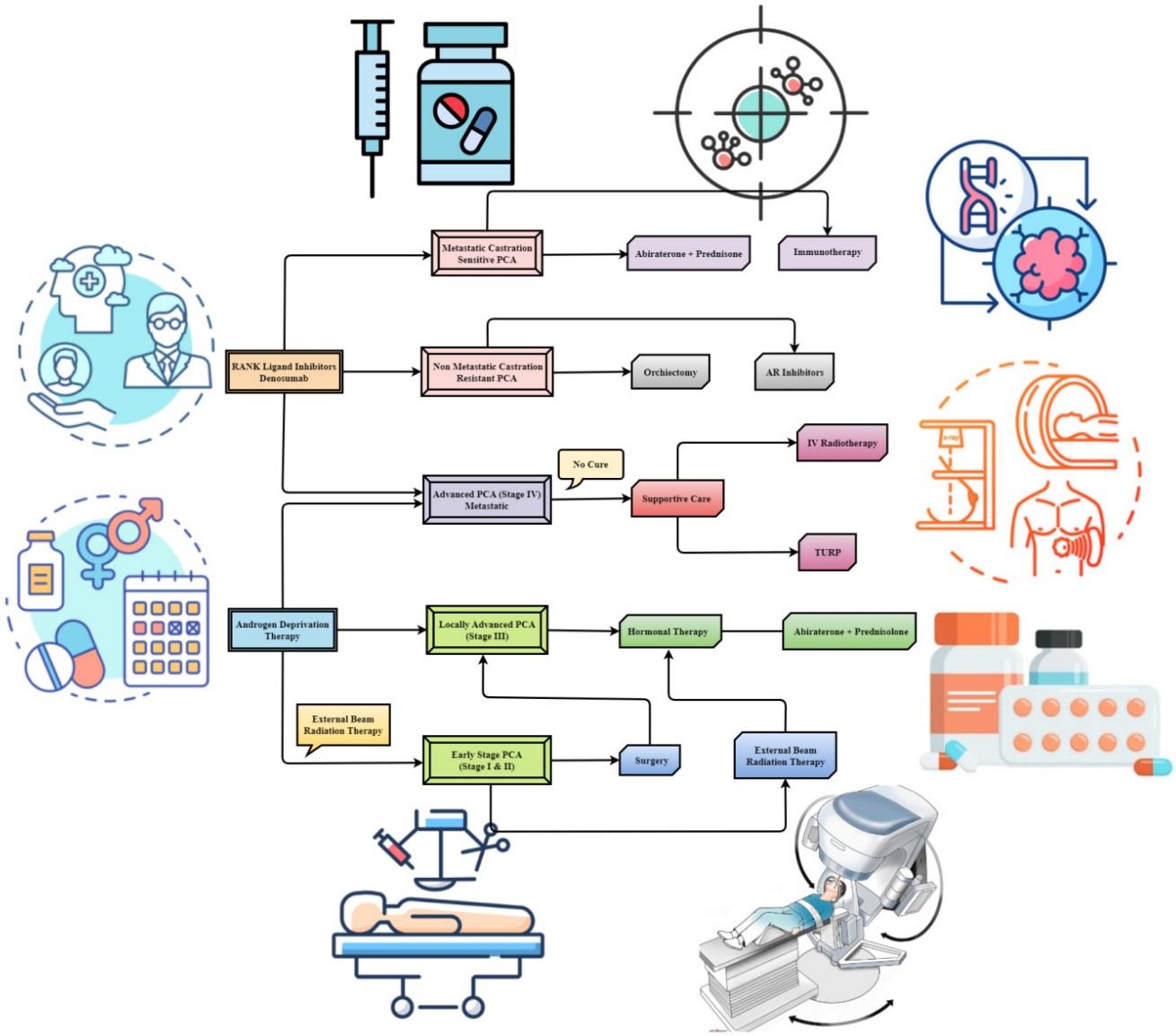

Figure 1. Phased approach to Prostate Cancer (PCA) treatment.

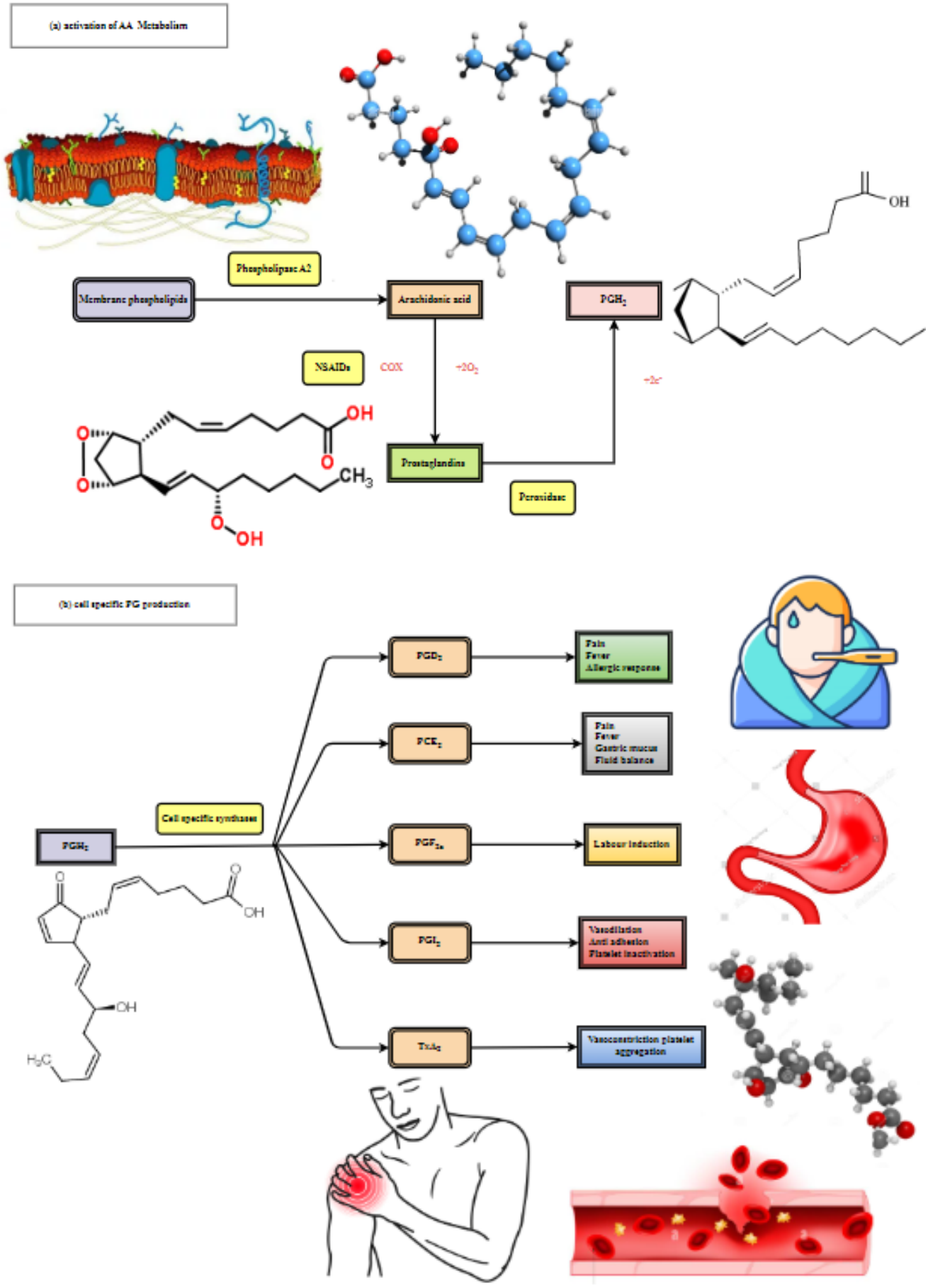

Figure 2. Prostaglandin production via cyclooxygenase (COX)-1 and - 2 isoform catalysis from membrane-bound arachidonate.

promoting PGE2 while preserving the synthesis of gastroprotective chemicals unaffected by habitual COX (Saxena et al,2020). To produce selective COX-2 inhibitors, understanding the structure of COXs was crucial. Research revealed that the locations interacting with inhibitors in COX-1 and COX-2 were structurally identical and highly stable (Curry et al,2019). By altering one amino acid in COX-2 (Val to Ile), its inhibitory effect shifted from resembling COX-2 to that of COX-1 for COX-1 selective inhibitors. This indicates that the presence of Val at location 509 creates space for selective electrostatic bonds among molecules, fitting into the enzyme's active site (Fife et al,.2004).

During the process of transformation and renewal, Cancer Stem Cells (CSCs) are believed to originate from established adult cells, localized stem cells, or embryonic stem cells. Various factors, including illnesses, harmful substances, or treatments like chemotherapy, can trigger or accelerate this conversion during tissue regeneration (Rosen and Jordan, 2009). The uncontrolled proliferation resulting from oncogenic amplification and inactivation of cancer suppressors leads differentiating cells to disintegrate and acquire stem cell traits (Kelly et al., 2007). Due to their unlimited proliferating capacity, embryonic cells and their descendants are particularly susceptible to mutation and irregular cell division with even minor changes in their genome. Given their high immunity, Cancer Stem Cells (CSCs) evade conventional cancer therapy, suggesting inevitable metastasis and tumor regrowth. Combining targeted removal of CSCs with standard radiation therapy enhances effectiveness and outcomes by significantly reducing tumors due to CSCs' remarkable adaptability (Mani et al., 2008). Identifying distinct CSC surface markers and profiling CSCs from prevalent tumor populations facilitates the development of focused approaches for CSC elimination. This study underscores the potential of targeting cancer-causing cells as a treatment option for various malignancies (Singh et al., 2003). Tumor growth and recurrence are attributed to CSCs' genetic makeup, characterized by self-sustaining abilities, differentiation into specialized cell types, tumor spread, and metastases (Clevers, 2006). CSCs possess a fundamental self-renewal characteristic, generating both additional stem cells and more differentiated tissue through asymmetric multiplication. Regulating this regenerative property presents a potential therapeutic avenue, as CSCs' inclination for regeneration is a significant factor in tumor formation. CSCs can develop into specific cell categories and morph into various cell types, regulated by pathways associated with Wingless integrating site (Wnt), Sonic Hedgehog (Hdhg), and Patch, contributing to self-regeneration and diversification.

Carcinoma occurs when cancerous tumors spread from their original site to other organs or tissues through the blood or lymph systems. Accumulated mutations, resulting from changes in cancer-causing genes that suppress tumors (Hoey et al., 2009) and proteins involved in DNA repair pathways, lead to unchecked growth and cancer. Without medical intervention, the disease progresses, and the body initiates a metastatic cascade, increasing the chances of survival. Despite medical care, Cancer Stem Cells (CSCs) can contribute to tumor resurgence due to their resistance capabilities (Ginestier et al., 2010). The activation of Epithelial-Mesenchymal Transition (EMT) promotes the spread of tumor cells, and CSCs play a significant role in this process. By creating a conducive growth environment that facilitates blood vessel formation, cancer cells influence metastatic cascades through connections to the biological components of the tumor's surrounding environment (Card et al., 2008). Effective tumor treatment relies heavily on targeted interventions in specific cell signaling pathways believed to influence cancer progression (Lin et al., 2008) , as well as the regenerative mechanisms of cancer origins and the maturation capacity of CSCs in the emergence of differentiated tumor tissue (Yu et al., 2007). This section briefly explores some of the key aspects illustrated in Figure 3.

An intricate biological mechanisms of chemotherapy resistance is shown in Figure 4. For tumor-fighting drugs, including those considered inherently cancer-promoting, to be effective in clinical trials (Lin et al., 2008), they typically require chemical activation through the CYP cytochrome P450 system, the glutathione-S (GST) superfamily, or the urea kinase (UGT) superfamily (Chin et al., 2009). However, malignancies and Cancer Stem Cells (CSCs) may develop resistance to chemotherapy due to mutations altering their metabolic capabilities, reducing the drug's effectiveness (Martinez & Gregory, 2010). Changes in cell-killing proteins, such as the cancer-fighting gene p53 (TP53), present another avenue for developing tolerance through drug deactivation. Half of tumors carry TP53 variants rendering it nonfunctional, leading to cancer resistance (Takamizawa et al., 2004). In chemoresistance, inhibitors of p53, including apoptotic proteolysis activation factor 1 (Apaf-1) and caspase-9, are compromised (Li et al., 2008).

Certain chemotherapy drugs target DNA, inducing apoptosis through deleterious chromosomal crosslinks, as seen with Cisplatin. However, resistance can emerge if drug targets undergo modified treatment consequences due to mutations or altered expression levels (Zielske et al., 2011). Ovarian tumors develop tolerance to the chemotherapeutic drug Taxol due to polymorphisms in biological targets like beta-tubulin. High levels of the membrane proteins MRP1 in neuroblastoma and BCRP in small-cell lung cancers (Marson et al., 2008), also exhibited by stem cells, contribute to drug resistance. The efflux system, primarily involving ABC transporters, serves as a protective mechanism by removing drugs and toxins from healthy cells (Clevers, 2006). Nonetheless, it acts as a drug resistance process for malignancies, shielding cancer cells and CSCs from various first-

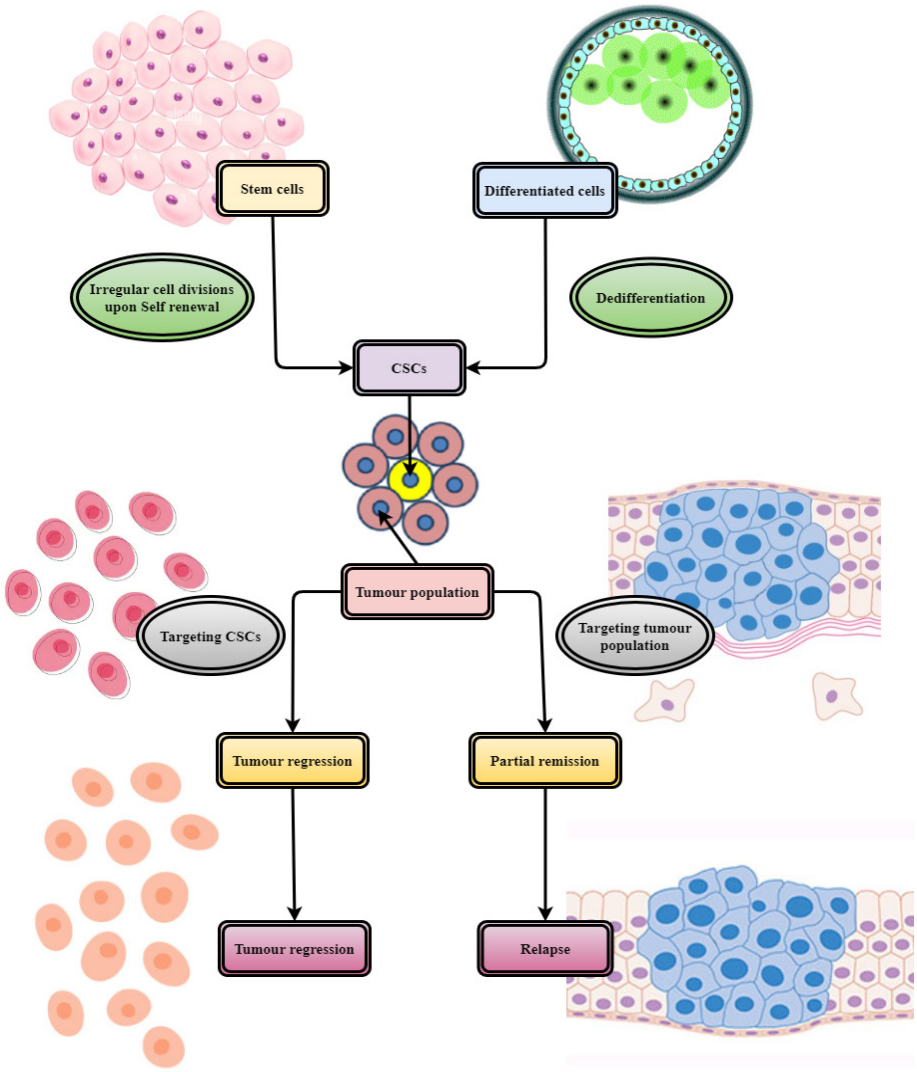

Figure 3. The cancer stem cell hypothesis and therapeutic strategy.

Box 1. Algorithm on Drug Repositioning and Response Detection

Input: two drug source images:D1, D2.
Step 1 : Remove reliance on a single source for image input pixels.
Step 2: Create a new matrix M by transforming each image into a set of column vectors.
Step 3: Determine A-Score using the formula.
Step 4: Produce a probability value of eigenvalues and a full matrix whose columns are the correspond eigenvectors.
Step 5: Learn how to calculate the fused weight by following these steps
Step 6: if ((D1) > D(2))
Step 7: D1 = /
Step 8: else
Step 9: D2 = /
Step 10: Combining two separate photos into one using the following calculation technique
Step 11: T = D1+ D2
Output: Tumored image T.

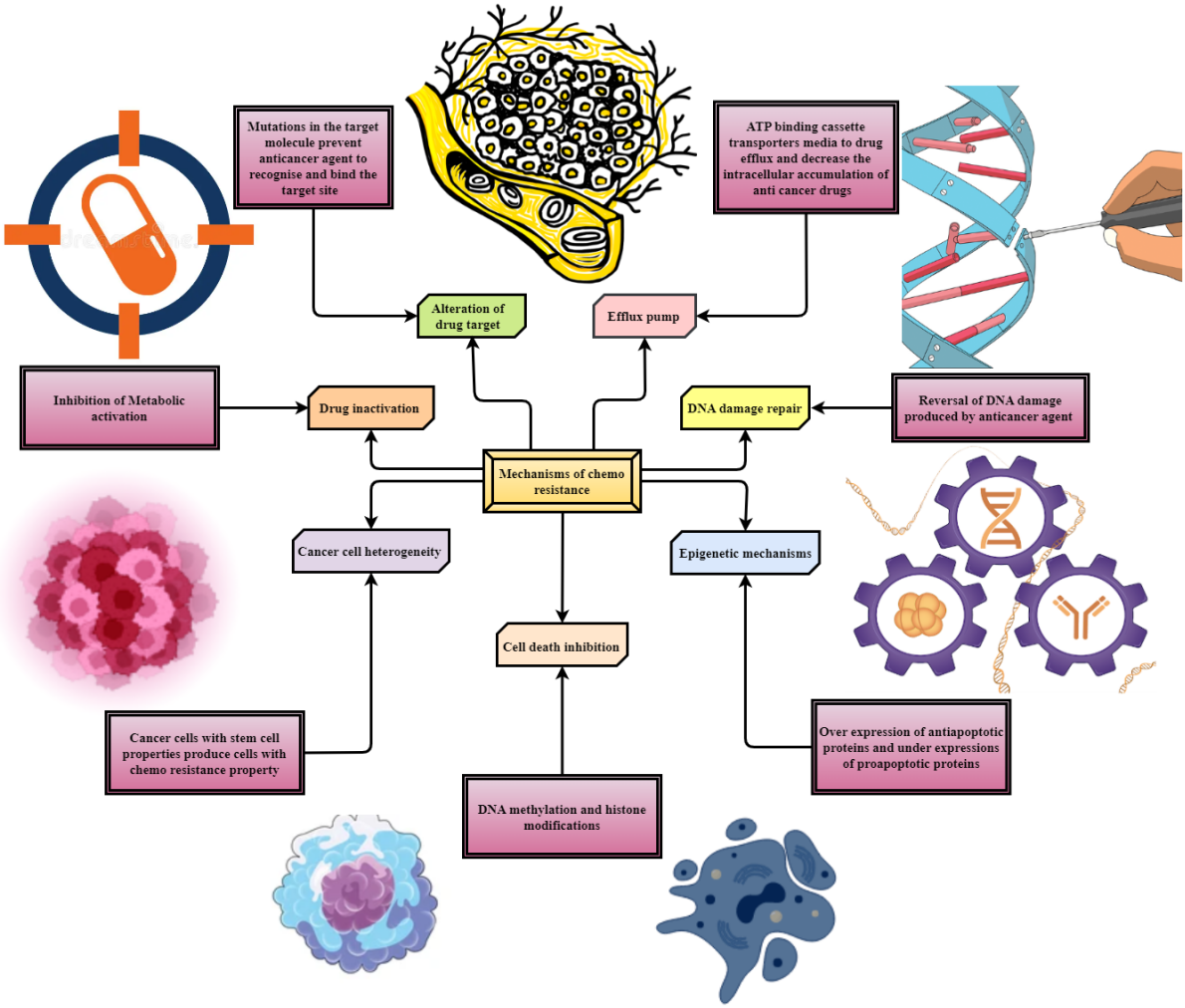

Figure 4. Chemical resistance mechanisms.

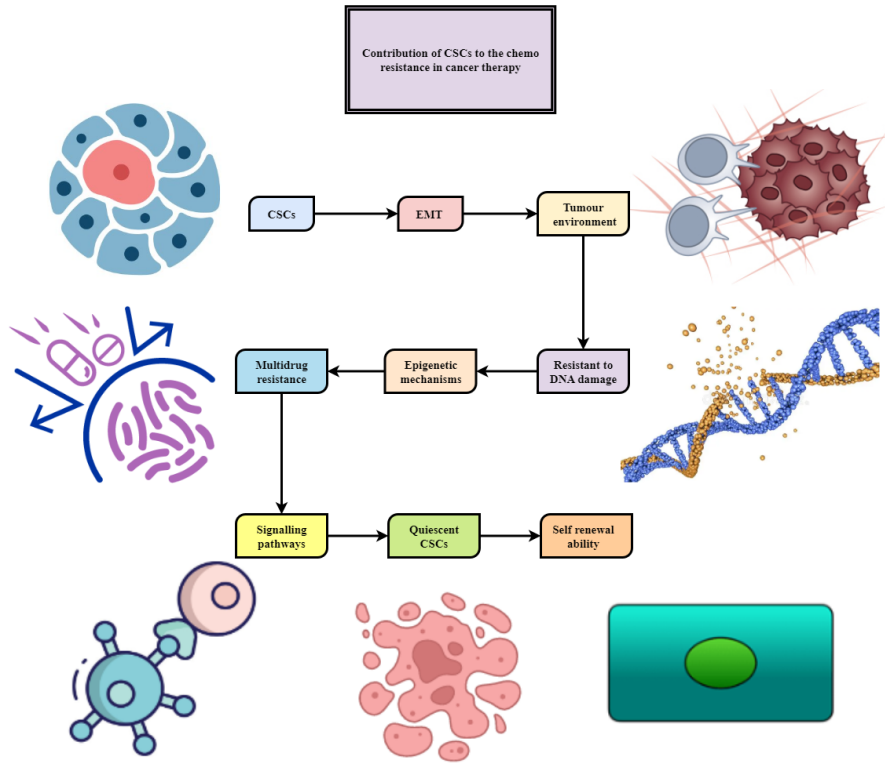

Figure 5. Resistance to treatment and spread of cancer in part to CSCs.

line chemotherapy drugs (Chiba, 2006). To counteract drug-induced DNA destruction, activities influencing the DNA repair processes of nucleotide excision and recombination between genes may reverse the therapeutic effects of chemotherapy (Lapidot et al., 1994).

Therefore, it is suggested that making chemotherapy more efficient involves combining it with the inhibition of repair mechanisms. Cell death is regulated through various means, including apoptosis and autophagy. Alterations in the expression and control of apoptotic pathways can enhance susceptibility to anticancer drug therapies that induce cell destruction (Houbaviy et al. 2003).

Cancer stem cells (CSCs) exhibit resistance to chemotherapy and radiation, playing a crucial role in various cancers, including pancreatic, breast, colon, and brain cancers. Recent research focuses on CSCs, revealing their role in producing progenitor cells that contribute to cancer spread and relapse despite treatment. Genetic drugs targeting progenitor cells can reduce metastases. Understanding how CSCs contribute to drug tolerance improves chemotherapy efficacy and reduces relapses (Rosen & Jordan, 2009) Figure 5 outlines mechanisms through which CSCs resist therapy and promote cancer spread, responding to and influencing the tumor microenvironment. Various elements in the CSC habitat, such as endothelial cells, immune cells, and growth-promoting agents, support CSCs' primitive nature (Takahashi & Yamanaka, 2006). Hypoxia in the tumor environment sustains CSCs, linked to malignant recurrence and resistance to multiple drugs through HIFs (hypoxia-inducible factors). HIF-2 and Oct4 play roles in CSC self-sustainment, while Sox2 modulates Oct4 levels. Oxygen deprivation protects CSCs by reducing reactive radicals, promoting cancer proliferation and resistance to therapies. HIFs influence pathways to maintain CSCs in a dormant phase (Reinhart et al., 2000).

Cancer stem cells (CSCs) efficiently produce protein transporters, with cancer cell markers like adenosine (ALDH) reducing oxidative damage and enhancing resistance to taxanes and rhodium-based treatments (Lapidot et al., 1994). ALDH also provides protection against radiation by neutralizing harmful substances from exposure. DNA damage and apoptosis are common effects of chemotherapy and radiation, but CSCs activate DNA repair pathways, ensuring their survival (Celia-Terrassa et al., 2012). Epithelial-mesenchymal transition (EMT) in cancer involves cells losing their properties, driven by various signals like growth factors and hypoxia. Tumor cells in multiple EMT stages are more invasive, pass through collectively, and express mixed genes (Zhao et al., 2010). The proposed role of EMT in cancer progression and metastasis emphasizes the importance of understanding its influence for effective cancer treatment.

Overall, Cancer stem cells (CSCs) exhibit resilience to chemotherapy and radiation, playing a significant role in various cancers. Suspected of causing drug resistance in pancreatic, breast, colon, and brain cancers, CSCs are a focus of recent research. Despite treatment and cancer cell destruction, CSCs contribute to metastasis and relapse (Marson et al., 2008).. Figure 5 illustrates mechanisms of CSCs resisting therapy and promoting cancer spread. Understanding CSCs' role in drug tolerance aids improved cancer treatment. CSCs influence the tumor microenvironment, facilitating growth, differentiation, and resistance to therapies like chemotherapy and radiotherapy. Factors like hypoxia, cytokines, and tumor-fighting drugs contribute to epithelial-to-mesenchymal transition (EMT), influencing tumor progression and resistance to chemotherapy. An improved understanding of EMT's role is crucial for effective cancer treatment (Diehn and Clarke, 2006).

Drug repositioning and response detection based on algorithm

Utilizing randomized control trials (RCTs) for cancer treatment, the equation for drug repositioning and response detection can be expressed as follows:

Drug Repositioning = f (RCT Data, Machine Learning, Patient-specific Information)

This equation involves leveraging RCT data, employing machine learning techniques, and considering patient-specific information to identify new and effective drug positions for cancer treatment while monitoring treatment responses.

Researchers developed an algorithmic approach to repurpose medicines for new therapeutic uses by analyzing connections between drugs and diseases. Ratings ranging from +1 to -1 indicate the effectiveness of each medicine-disease combination. If a medication's most negative rating corresponds to a different group of modifications in response to exposure, it may have therapeutic potential. Some studies shows the drug similarity scores calculated using CMap drug expression patterns and preconditioned expression data for prostate and breast tumors (Lin et al,2015). The analysis focused on drugs with p-values below 0.05 after correction for false discovery rate (FDR) (Omura et al,2004). The items were then categorized based on enhancement ratings, with the most significant negative score indicating promising therapeutic possibilities. Validation of medication repurposing used sensitivity-dependent validation (SV) and the normalization discounting cumulative gain (OHED) (Iorio et al,2010). OHED scores were calculated using specific formulas, emphasizing the importance of sensitivity in analytical verification. Top-ranked medications were considered more interesting for therapeutic use.

Researchers also explored specific medications that could counteract the adverse effects of diseases. For instance, some algorithms use A-score, representing chemical bonds between a

medication and adjacent DE genes, was calculated and transformed into a probability value using standard deviation (Ren et al,2010). The Drug Repositioning and Response Detection algorithm involved creating a new matrix, determining A-Score, and calculating fused weights for comparing and combining images. Gene rankings were calculated using PageRank, and equations blended the differential expression of genes in illness and medication-related pathways (Smyth et al,2005). The PageRank algorithm, a modification of the random walk algorithm, was employed to assess network centrality. Damping values were experimented with, and 0.75 was determined as the ideal amount.

4. Use of Bayesian Network response detection in randomized control trials

When using Bayesian Network response detection in randomized control trials (RCTs), assessing robustness and reliability is crucial (Balshem et al,2011.). Sensitivity analysis systematically evaluates how changes in input parameters impact the network's structure, predictions, and response detection. This analysis helps understand response detection conditions, validate findings, and identify model limitations, contributing to a comprehensive understanding of uncertainties for better decision-making. Bayesian Networks for RCT-based response detection incorporate inference and prediction as core components (Guyatt et al,2013). Bayesian inference deduces probabilistic correlations between variables using observed data and prior knowledge, calculating posterior probabilities for likely response outcomes and influential factors. Predicting future responses enhances the practicality of Bayesian Networks, allowing better selection of patients for treatment strategies and contributing to personalized medication plans. This foresight improves cancer treatment accuracy, leading to better patient outcomes and more efficient healthcare resource utilization.

Sensitivity analysis is an essential tool for evaluating the robustness and reliability of Bayesian Network response detection models in RCTs (Newton et al,2007.). It involves systematically adjusting input parameters to observe changes in the network's structure, predictions, and response detection results. The goal is to determine how small changes in parameters affect the model's output, enhancing understanding of factors influencing response detection, ensuring findings' consistency, and identifying model flaws.

Different factors are essential to optimize the Bayesian Network response detection. Accuracy is a key performance indicator for Bayesian Network response detection in RCTs. Evaluating prognostic accuracy involves comparing the model's forecasts with actual RCT results. Other performance parameters, such as sensitivity, specificity, positive predictive value, and negative predictive value, contribute to a comprehensive evaluation (Tang et al,2012). Considering these measures alongside accuracy provides a more robust assessment of the model's efficacy, leading to more reliable cancer treatment regimens. Conditional probability plays a vital role in Bayesian Network response detection using RCT data. It enables probabilistic reasoning by quantifying the likelihood of treatment success based on specific variables within the network. Conditional probability allows for personalized medicine, as it considers a patient's unique profile and influencing factors in treatment response (Spiegelhalter et al,1993). This paradigm optimizes treatment regimens and improves patient outcomes in the context of RCT-based Bayesian Network response detection. Causal inference analysis is crucial for Bayesian Network response detection in RCTs, exploring causal links between variables to understand determinants of treatment response. This goes beyond simple correlation methods, providing insights into underlying causal mechanisms and allowing for more targeted and efficient cancer treatment plans.

Bayesian Networks, with their inference and prediction capabilities, offer a powerful framework for RCT-based response detection (Assareh et al,2011). These models enhance decision-making, improve treatment accuracy, and contribute to the advancement of personalized medicine in cancer therapy.

5. Conclusion

Drug repositioning is a transformative shift with profound implications for healthcare and pharmaceutical industries, particularly in cancer treatment. Quickly identifying existing drugs for repurposing in the fight against cancer is crucial, and drug repositioning offers a rapid and cost-effective solution. Traditional drug development faces challenges of lengthy timelines and high costs, necessitating alternative strategies. Overcoming the challenges of drug repositioning requires integrating diverse data sources, precise patient classification, and developing reliable response detection algorithms. To address these challenges, this review highlights the strength of randomized controlled trials (RCTs) to assess medication effectiveness in different cancer subpopulations. RCTs provide a structured and systematic framework for evaluating and discovering new drug candidates. By combining RCTs with modern data analytics and machine learning, the study introduces the Bayesian Network Response Detection based on Randomized Control (BNRD-RC). This approach not only predicts patient responses and refines treatment regimens but also unveils potential new avenues for cancer treatment. It expands drug repositioning by examining pharmaceutical synergy and combination therapy for rare cancers. Simulation analysis plays a vital role in validating the placement of drugs, evaluating treatment outcomes, and assessing simulated clinical scenarios. This comprehensive approach allows for a

holistic understanding of the potential benefits and risks of drug repositioning in cancer treatment. The integration of drug repositioning with RCTs, advanced analytics, and simulation analysis marks a pivotal moment in cancer therapies. It has the potential to revolutionize treatment, enhance patient outcomes, and optimize healthcare spending, while also accelerating the drug discovery process.

Author Contributions

A.C. conceptualized, and wrote, C.K. performed the data analysis, validation and revised the article.

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None declared.

Competing financial interests

The authors have no conflict of interest.

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