

EVALUATING CANCER DRUG-TARGETING PATHWAYS WITH LARGE LANGUAGE MODELS

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ABSTRACT

Integrating artificial intelligence into drug discovery holds great potential for prioritizing therapeutic targets. This study presents a novel framework combining bioinformatics tools and AI-driven evaluations to streamline target identification. Using pancreatic adenocarcinoma (PAAD) as a case study, we analyzed 252 candidate genes and associated pathways derived from the PAGER database. ChatGPT-4o evaluated pathways by scoring them across seven categories using structured prompts and weighted criteria to ensure robustness. Our approach demonstrated a statistically significant differentiation between PAAD-related and unrelated pathways ($t(489)=-12.06$, $p<0.00001$, Hedges' $g=1.24$). Top-ranking pathways included the pancreatic cancer and pancreatic adenocarcinoma pathways. Candidate genes were ranked using normalized pathway significance and gene-specific contributions, combined into a weighted formula. This approach highlighted key targets including AURKB, POLA1, and RRM2. These findings highlight the potential of generative AI to automate and accelerate target discovery, offering an adaptable methodology for diverse therapeutic areas.

KEYWORDS

Pancreatic adenocarcinoma, drug target validation, ChatGPT-4o evaluation framework, oncology drug development

1. INTRODUCTION

This study presents a novel framework combining bioinformatics tools and AI-driven evaluations to streamline target identification. Using pancreatic adenocarcinoma (PAAD) as a case study, the framework was designed to systematically evaluate and rank therapeutic targets. While PAAD was selected due to its clinical significance and treatment challenges, the methodology is easily adaptable to other diseases, demonstrating its potential to advance drug discovery across diverse therapeutic areas.

Pancreatic adenocarcinoma is a highly aggressive solid tumor that constitutes over 90% of all pancreatic cancer cases [1]. Pancreatic ductal adenocarcinoma (PDAC) is a common subtype of PAAD, although these terms can be used interchangeably. PAAD is one of the most challenging malignancies to treat, with a 5-year survival rate of less than 10% [2], and it currently ranks third in cancer-related deaths in the United States, with projections indicating it will become the second-deadliest cancer by 2030 [3], [4].

PAAD is commonly characterized by its poor prognosis and ineffective treatment options. PAAD tumors progress rapidly without recognizable symptoms; at the time of diagnosis, over 80% of patients have experienced metastasis and spread of the disease, evidencing PAAD's poor prognosis and resulting in advanced tumors ineligible for surgery [5]. Standard treatments for PAAD, such as chemotherapy and immunotherapy, have failed to produce meaningful results measured by patient survival since the immunosuppressive and intensely desmoplastic tumor microenvironment in PAAD often limits tumor exposure to chemotherapy and attack by immune cells [6], [7]. For example, approved chemotherapies such as gemcitabine/nab-paclitaxel or FOLFIRINOX only improve survival by 2-4 months and are accompanied by severe toxicity and adverse effects [8].

Current targeted approaches to PAAD drug development have been researched extensively with the availability of cancer genomic sequencing data. For example, KRAS, which is mutated in nearly 90% of PAAD patient samples [9], has become a common target for investigational drugs. However, leading drugs involved in clinical trials for PAAD treatment, such as sotorasib, which targets the KRAS G12C mutation, have shown minimal survival improvements of around 3 months and also commonly exhibit adverse effects [10]. Therefore, recent research regarding PAAD drug targets has shifted towards genomic tumor drivers that are predominantly involved in PAAD signaling pathways as well as differentially expressed in tumor tissues [11], [12], [13].

This paper describes the bioinformatics process of ranking potential PAAD drug targets with a systematic, unbiased approach by evaluating their relation to PAAD. The approach that we developed has the following innovative characteristics. First, we performed a comprehensive pathway analysis to assess a drug target's relevance to PAAD progression and suitability as a novel target for PAAD treatment. Second, we leveraged ChatGPT-4o in our evaluation tasks to improve efficiency and demonstrate the utility of generative AI in de novo drug discovery. ChatGPT-4o is the latest iteration of the Generative Pre-trained Transformer Large Language Model developed by OpenAI, and is a potential tool to aid in de novo drug discovery through contributions in data interpretation, simulation, modeling, and more [14]. Finally, we streamline the drug discovery process by integrating this ChatGPT-4o evaluation with bioinformatic pathway and survival analysis.

2. METHODS

Our methodology was structured into five steps to systematically evaluate and prioritize candidate drug targets for pancreatic cancer targeted therapy. First, we curated a list of 252 candidate drug targets using PAGER, a bioinformatics platform that integrates pathway-associated gene sets to identify pancreatic cancer-relevant genes and pathways. Second, we retrieved biomolecular pathways associated with our candidate geneset using PAGER. Third, we utilized a novel evaluation framework generated by ChatGPT-4o to score each pathway, leveraging AI's capabilities to execute an unbiased analysis of pathway relevance and drug target suitability. Fourth, we calculated a baseline pathway score by evaluating unrelated pathways with the same framework, using ChatGPT-4o and PAGER to establish benchmarks for pathway significance. Fifth, we integrated pathway scores and individual gene scores to calculate weighted final ranking scores for each candidate gene. Next, we will describe the approaches in detail.

2.1. Candidate Cancer-Specific Drug Target Curation

We first manually compiled a list of candidate drug targets by searching for pancreatic cancer-related pathways, annotated lists, and gene signatures (PAGs) using PAGER (Pathway Annotated Gene Enrichment Ranking), which is a bioinformatics platform that identifies and

analyzes PAGs associated with a user-provided geneset. PAGER's robust prioritization algorithms and extensive coverage, including 113,830 PAGs from 37 data sources, allow it to uncover critical genes that other tools might overlook [15]. Additionally, its ability to integrate diverse datasets ensures a more holistic understanding of pathway relevance in complex diseases such as pancreatic cancer. From this search, we identified 252 genes that exhibited high prioritization scores within the resulting PAGs, forming our comprehensive initial candidate list.

2.2. Curation of Cancer-Affected Biomolecular Pathways

To rank the candidate drug targets, we established a comprehensive evaluation process that assessed each candidate in relation to PAAD. Our approach went beyond direct assessment of the drug targets; instead, we focused on retrieving and evaluating biomolecular pathways that are impacted in PAAD and pertinent to each candidate. This strategy was designed to ensure that candidates with limited research literature in the context of PAAD were not overlooked, thereby facilitating the discovery of novel drug targets [16], [17], [18], [19].

We employed PAGER to source pathways associated with each candidate within the context of PAAD. We then queried our initial candidate list in PAGER and compiled the resulting pathway-type PAGs with at least five genes overlapping with the candidate list. The threshold of five overlapping genes was used to filter pathways and control the number of pathways included for downstream analysis. This threshold was selected to balance comprehensiveness with relevance, ensuring pathways with sparse overlap were excluded while retaining those with significant biological context.

To focus on curated pathways, we filtered this pathway list by data source, excluding MSigDB and PharmGKB. This resulted in 363 PAAD-related pathways. These detailed findings are presented in Supplementary File 1.

2.3. Evaluation of Pathway Contribution to Cancer Progression Using Chatgpt-4o

We utilized ChatGPT-4o to develop a comprehensive evaluation framework to assess the significance and influence of specific biomolecular pathways in pancreatic cancer. Previous research has validated ChatGPT's consistent performance in evaluation tasks compared to human evaluators and its reliability in medical and biological contexts [14], [20], [21], making it an efficient and accurate tool for our analysis.

Ranking biomolecular pathways based on their relevance to specific diseases is a well-established bioinformatics and systems biology approach. Various studies have proposed scoring frameworks integrating multiple criteria, such as pathway relevance, genetic mutations, clinical biomarkers, and therapeutic potential. For example, Subramanian et al. [22] introduced the Gene Set Enrichment Analysis (GSEA) framework, which evaluates pathway significance based on differential expression patterns across gene sets. Similarly, Kanehisa et al. [23] used KEGG pathways to prioritize pathway significance in cancer by examining functional annotations and mutation frequencies.

The integration of ChatGPT-4o into our pathway evaluation process demonstrates how AI tools can augment traditional frameworks. ChatGPT-4o synthesizes and contextualizes information from diverse datasets, providing a streamlined approach to multi-criteria scoring. By using structured prompts to evaluate each pathway across defined categories, ChatGPT leverages existing literature and datasets to generate objective scores [24], [25], [26].

We employed a numerical scoring system to minimize potential errors such as hallucinations and ambiguities commonly associated with AI, fully detailed in Supplementary File 2. The ChatGPT-4o-generated framework evaluated each pathway across seven categories to assess its role in PAAD progression and its potential as a drug target. To evaluate each pathway, the pathway name and scoring system were inputted as prompts for ChatGPT-4o, which then provided the evaluation scores. These prompts were slightly varied between trials to ensure robustness and reduce the influence of prompt-specific biases, thereby improving the reliability of the evaluation scores. These varied prompts can be found in Supplementary File 2.

Each pathway was scored on a scale from 0 to 9 in each category, with 0 indicating no relevance or evidence and 9 indicating strong, well-supported significance. These scores were multiplied by specific weights assigned to each category based on their relative importance in determining a pathway's therapeutic potential.

Pathway relevance to PAAD was assigned the highest weight of 5 because it directly evaluates the pathway's involvement in PAAD-specific processes such as tumor initiation, progression, and therapeutic resistance, which are key factors in identifying actionable targets. Pathway relevance was evaluated by analyzing the pathway's documented involvement in key biological processes such as tumor initiation, progression, metastasis, and therapeutic resistance.

Target druggability, weighted at 5 to emphasize the practical feasibility of translating pathway findings into therapeutic strategies, assessed the presence of well-characterized, actionable drug targets within the pathway and the availability of drugs targeting these components. Pathways with multiple approved drugs or drugs in advanced clinical trials received higher scores, while those with hypothetical or preclinical targets received lower scores.

Genetic alterations in the pathway were given a weight of 4, due to its role in indicating the fundamental molecular drivers of PAAD and providing a foundation for stratifying and targeting patient subgroups. Genetic alterations was evaluated by examining the frequency and impact of mutations in pathway-associated genes among PAAD patients. Pathways containing genes with high mutation prevalence, such as KRAS or CDKN2A, received higher scores, especially if these mutations were linked to tumor progression or poor prognosis.

Biomarker availability was weighted at 4 because it is essential for tailoring treatments and monitoring therapeutic responses. It assessed whether the pathway was associated with reliable markers for patient stratification or treatment monitoring. Pathways with clinically validated biomarkers, such as CA19-9, received higher scores, while those with experimental or unvalidated biomarkers scored lower.

Resistance mechanisms, crucial for overcoming therapeutic challenges and improving clinical outcomes, were weighted at 4 and focused on the pathway's involvement in resistance to existing therapies for PAAD, such as gemcitabine or 5-FU. Pathways with strong evidence from clinical or preclinical studies linking them to therapy resistance scored higher, while those with minimal or inconclusive evidence scored lower.

Literature evidence helps contextualize findings but is inherently dependent on research focus, which may bias representation; therefore, it was weighted at 3. Literature evidence considered the depth and breadth of research supporting the pathway's relevance to PAAD. Pathways with extensive support from clinical trials or high-impact publications received higher scores, while those with limited or speculative evidence received lower scores.

Lastly, the safety profile, weighted at 3 since it may be less determinative in early-stage target identification than other metrics, evaluated the feasibility of targeting the pathway based on

known or anticipated side effects. Pathways associated with well-tolerated therapeutic interventions scored higher, while those with significant toxicity concerns or off-target effects received lower scores.

The total score for each pathway was calculated by summing the weighted scores across all categories, and these totals were used to rank pathways according to their overall potential as drug targets. The scoring process was repeated twenty times for each pathway, and an average score was taken to find the final ranking score for each pathway.

To ensure robustness, we evaluated the scoring framework's sensitivity to changes in category weights. Pathway relevance and druggability weights varied by $\pm 10\%$, but the overall rankings remained consistent for the top 10 pathways, demonstrating stability in scoring.

2.4. Establishment of Pathway Evaluation Baseline Score Using Cancer-Unrelated Pathways

To provide a reference point for pathway evaluation, we generated a list of random genes not included in our candidate gene list using ChatGPT-4o. This gene list, “unrelated genes,” was subsequently queried in PAGER to identify 129 pathways unrelated to PAAD, termed “unrelated pathways.”

The ChatGPT-4o scoring system was applied to each unrelated pathway using the same methodology employed for PAAD-related pathways. Each pathway was evaluated 20 times, and the average score across all trials was calculated to determine the final ranking score for each unrelated pathway. The final scores of all unrelated pathways were then averaged to establish the pathway baseline (PB) score, which served as a benchmark for assessing the significance of pathways in the context of PAAD.

2.5. Integration of Pathway and Gene Contributions to Rank Candidate Genes

Each candidate gene's membership in previously evaluated pathways was systematically recorded. This was accomplished by examining the “PAG Members” table associated with each pathway in the PAGER database. Two distinct scores were assigned for every instance of a gene being part of a pathway: the Rank Prioritization Pathway (RPP) score and the Rank Prioritization Gene (RPG) score. The RPP score was derived by dividing the pathway ranking score, obtained through ChatGPT-4o's evaluation, by the pathway's baseline score. This calculation standardizes the pathway's significance relative to its baseline. The RPG score corresponded to the rank prioritization score of the gene within the specific pathway, as provided by the PAGER database. This score directly reflects the gene's importance or contribution to the pathway. Both the RPP and RPG scores were subsequently normalized on a scale from 0 to 1 using the following formula:

$$z_i = (x_i - \min(x)) / (\max(x) - \min(x))$$

The final score for each gene-pathway combination was calculated using a weighted formula, with the RPP score contributing 20% and the RPG score contributing 80%. To consolidate all instances of a gene across PAAD-related pathways, the average final score for all instances was calculated to derive the gene's overall ranking score. This comprehensive approach ensures a balanced assessment of pathway-level and gene-specific contributions, effectively prioritizing genes that demonstrate significance within the most impactful pathways.

3. RESULTS

The results section presents a detailed analysis of pathways and genes associated with pancreatic adenocarcinoma (PAAD). By leveraging a robust scoring framework, this study aims to identify and rank pathways and candidate genes based on their relevance to PAAD progression and therapeutic potential. Key findings highlight the significance of specific pathways and genes in PAAD-related mechanisms, as described below.

3.1. ChatGPT- Driven Analysis Prioritizes Biologically Valid Pathways in PAAD

Figure 1 highlights the top 20 pathways identified through our pathway evaluation, ranked by their average final scores. The top three pathways, "Pancreatic cancer" (224.6), "Pancreatic adenocarcinoma pathway" (221.7), and "hsa05212 Pancreatic cancer (Homo sapiens)" (214.7), underscore the strong association of these pathways with PAAD progression and therapeutic relevance. These pathways integrate key signaling mechanisms, such as PI3K/Akt and MAPK signaling, which are also independently ranked highly in the analysis. The prominence of pancreatic cancer-specific pathways in the rankings validates the scoring framework and emphasizes the biological relevance of these pathways in driving PAAD progression, survival, and resistance mechanisms. A complete list of pathways and their scores is provided in Supplementary File 1.

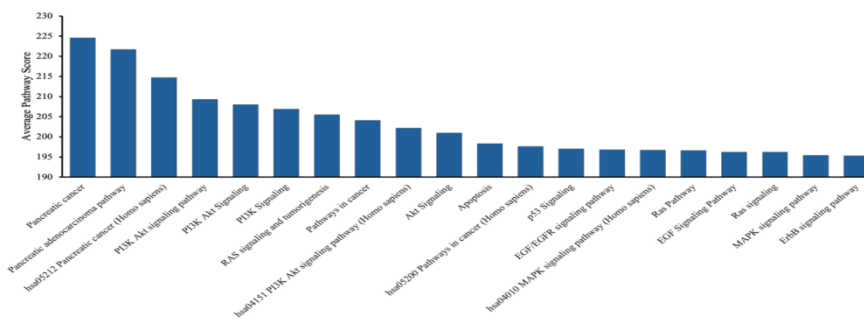


Figure 1. Top 20 related pathways from ChatGPT-4o evaluation

3.2. Comparison of Cancer-Related and Unrelated Pathway Evaluations

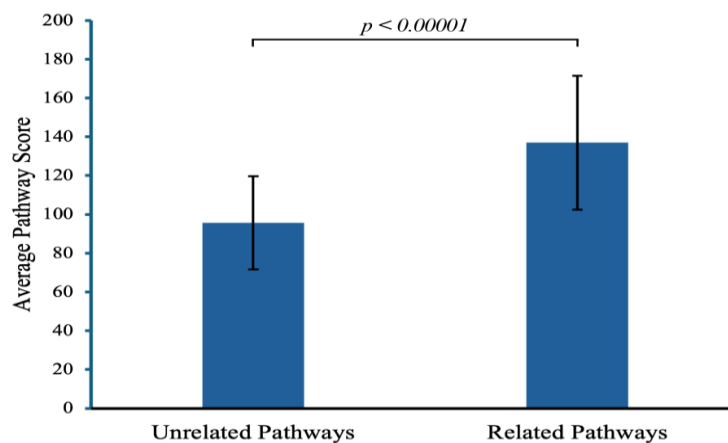


Figure 2. Comparison of PAAD-unrelated and related pathway scores.

Figure 2 visually illustrates the differences in mean scores and variability between the two groups, highlighting the significantly higher scores for PAAD-related pathways. We conducted a two-sample independent t-test to compare the mean scores between unrelated pathways ($M = 95.69$, $SD = 22.67$) and PAAD-related pathways ($M = 137.00$, $SD = 36.48$). The t-test revealed a significant difference between the two treatments ($t(489) = -12.06$, $p < .00001$), indicating that the PAAD-related pathways had a significantly higher mean score compared to the unrelated pathways. The calculated pooled variance (s_p^2) was 1117.2. The full rankings of PAAD-related pathways are provided in Supplementary File 1, and unrelated pathways in Supplementary File 3.

To quantify the magnitude of this difference, we calculated Hedges' g , which accounts for the two groups' unequal sample sizes ($N_{\text{unrelated}} = 129$, $N_{\text{related}} = 363$). The effect size ($g = 1.24$) indicates a significant difference, emphasizing the greater relevance of PAAD-related pathways compared to unrelated pathways.

3.3. Ranked Candidate Genes in PAAD-Related Pathways

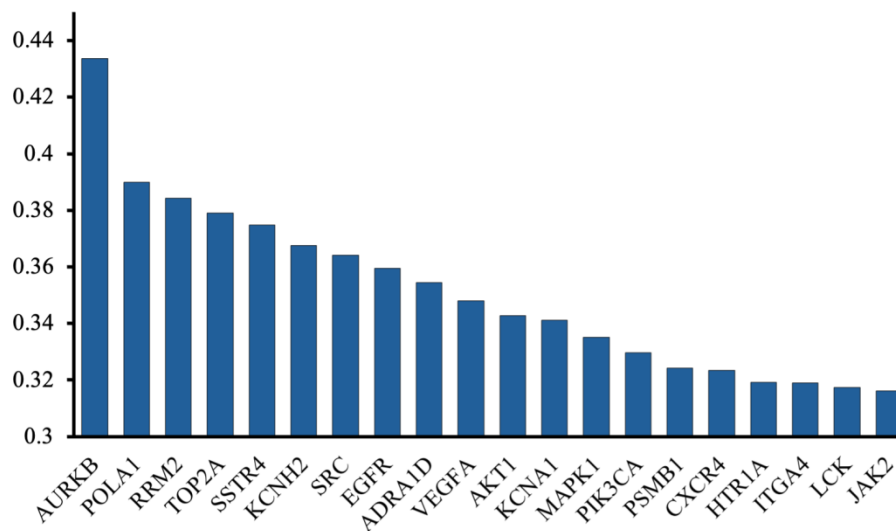


Figure 3. Top 20 candidate genes ranked by average final score in PAAD-related pathways

Following the scoring and ranking process for the 252 candidate genes, the integration of Rank Prioritization Pathway (RPP) and Rank Prioritization Gene (RPG) scores allowed for a comprehensive evaluation of gene significance within PAAD-related pathways. Figure 3 highlights the top 20 candidates, representing the genes with the most substantial and consistent contributions to high-scoring pathways critical to PAAD progression and therapeutic resistance. A complete list of ranked genes is provided in Supplementary File 4.

The top-ranked gene, AURKB, achieved an average final score of 0.4336, indicating its critical involvement in high-priority pathways linked to PAAD progression. Other highly ranked genes include POLA1 (0.3900), RRM2 (0.3843), and TOP2A (0.3791), all of which play key roles in cell proliferation and genomic stability, processes heavily implicated in PAAD tumorigenesis. Additionally, several genes with less explored roles in PAAD, such as SSTR4 (0.3749), KCNH2 (0.3676), and SRC (0.3641), emerged as high-ranking candidates, suggesting novel avenues for future research.

The gene ranking results closely align with our pathway analyses, reinforcing the biological significance of these findings. For instance, EGFR, a highly ranked gene with an average final score of 0.3595, is part of the well-characterized PI3K/AKT signaling pathway, ranked among our evaluation's top pathways. Genes such as AKT1 (0.3428) and PIK3CA (0.3297) were closely tied to the top-ranking PI3K Akt signaling pathway (209.3), highlighting their role in cell proliferation and survival. Furthermore, VEGFA (0.3480), critical for angiogenesis, aligns with pathways like Ras signaling (196.2) and MAPK signaling pathway (195.4), known to drive tumor progression. Additionally, MAPK1 (0.3351) strongly correlates with the MAPK signaling pathway, further reinforcing its role in oncogenic signaling. These associations underscore the integration of gene and pathway analyses in identifying biologically relevant targets for PAAD, providing a robust framework for prioritizing therapeutic interventions.

Sensitivity analysis confirmed that minor weight changes did not significantly impact pathway rankings. For example, a 10% reduction in the weight of pathway relevance shifted rankings by 3.87% (Supplementary File 5), demonstrating the reliability of the scoring framework.

4. DISCUSSION

In this study, we developed a novel framework for prioritizing therapeutic targets in pancreatic adenocarcinoma, focusing on biologically relevant pathways rather than relying solely on genetic mutation prevalence. This framework incorporates human-designed metrics, such as pathway relevance, druggability, and biomarker availability, alongside AI-driven evaluations to ensure a systematic, reproducible, and statistically significant assessment of potential drug targets. We leveraged AI's computational power by integrating ChatGPT-4o into this process while mitigating its inherent biases through iterative scoring, curated datasets, and human oversight.

Our framework emphasizes statistical rigor and transparency in scoring pathways. Each category, such as pathway relevance to PAAD or target druggability, was carefully weighted to reflect its importance in determining therapeutic potential. A key innovation in this framework is our use of ChatGPT-4o, which systematically evaluates pathways across multiple categories, accelerating the target identification process. However, we addressed potential biases in AI outputs by repeatedly scoring pathways and ensuring human-designed metrics were the foundation of AI prompts. These measures helped make the framework less susceptible to biases arising from incomplete training data or model oversimplification. The integration of ChatGPT-4o into our evaluation framework underscores the practical utility of AI in systematically identifying and prioritizing drug targets in pancreatic adenocarcinoma. ChatGPT-4o facilitated the efficient analysis of large, complex datasets, including TCGA and UALCAN, enabling a structured assessment of biologically relevant targets [27], [28]. This AI-driven approach allowed for rapid evaluation across predefined metrics like pathway relevance, druggability, and biomarker availability, significantly accelerating the target discovery process.

The integration of ChatGPT-4o into our pathway evaluation framework highlights the growing potential of AI tools in biomedical research. While ChatGPT-4o provides robust natural language processing capabilities, future iterations of the framework could benefit from advancements in AI technology. Emerging versions of ChatGPT and complementary AI tools, such as specialized models for bioinformatics or drug discovery, could enhance the precision and contextual accuracy of pathway evaluation. For instance, integrating AI tools trained specifically on biomedical datasets, such as PubMed abstracts or clinical trial repositories, could reduce reliance on general-purpose models and improve relevance to the domain. Additionally, combining ChatGPT-4o with AI-powered tools for molecular docking, systems biology simulations, or multi-omics analysis could provide a more holistic evaluation of pathways,

considering both computational and experimental data. These enhancements would enable more nuanced insights, such as identifying novel druggable targets, elucidating cross-pathway interactions, or prioritizing pathways for experimental validation. As AI tools evolve, their integration with traditional bioinformatics approaches holds promise for transforming how complex biological systems are analyzed and understood.

However, the limitations of AI-driven methodologies must be acknowledged to contextualize their findings. The accuracy of AI outputs is inherently tied to the quality, diversity, and representativeness of its training data. While this study utilized curated datasets such as PAGER to reduce biases, the underrepresentation of specific pathways or populations—such as those of rare subtypes of PAAD or from non-Western demographics—may still influence results [28]. Furthermore, AI frameworks often simplify complex biological interactions [29]. For example, while the weighted scoring approach used here allowed for a structured evaluation of pathways, it did not fully capture the intricate interplay of tumor microenvironment factors, such as stromal-epithelial signaling, or the dynamics of therapy-induced resistance mechanisms. This highlights the need for additional layers of validation.

Ultimately, this study's application of AI emphasizes the need for robust experimental validation and clinical trials to bridge the gap between computational predictions and actionable therapies [13], [30]. This study lays a foundation for future research, combining computational efficiency with experimental rigor to advance the development of impactful therapies for PAAD.

Despite these limitations, the versatility of the framework allows it to be adapted for evaluating pathway relevance in other cancer types and complex diseases. By tailoring the scoring categories and weights to reflect disease-specific characteristics, this methodology could be applied to diseases such as breast cancer, lung cancer, or neurological disorders. The ability to streamline multi-criteria evaluations using AI tools like ChatGPT-4o demonstrates its potential as a scalable approach in systems biology and precision medicine.

Our findings also highlight a crucial aspect of cancer target selection: the significance of targeting overexpressed or hyperactivated genes rather than frequently mutated ones. Many top-scoring targets, including EGFR, VEGFA, SRC, PIK3CA, and MAPK1, predominantly show high differential expression or hyperactivity in PAAD. This observation is critical, especially considering that cancer progression often involves both driver and passenger mutations, leading to genetic instability. Thus, targeting these overexpressed genes might offer more strategic advantages, particularly in later stages of PAAD, where mutations like those in KRAS are prevalent but may not be as actionable due to the complexity of the genetic landscape at these advanced stages.

5. CONCLUSIONS

In conclusion, our integrated approach combines bioinformatics and AI-driven evaluations to present a powerful model for advancing drug discovery in oncology. While this study systematically prioritized drug targets using bioinformatics and AI, experimental validation remains essential to confirm the identified genes and pathways' biological relevance and therapeutic potential. Future studies should focus on *in vitro* and *in vivo* experiments to validate top-ranked pathways like AURKB and EGFR and assess their potential in preclinical models. Integrating survival analysis with clinical sample cohorts would further substantiate these findings. Additionally, this framework can be further refined through collaborative efforts between computational and experimental teams to provide impactful therapeutic solutions for PAAD.

SUPPLEMENTARY FILES

The original data and supplementary information presented in the study are openly available in Zenodo at <https://doi.org/10.5281/zenodo.14542583>.

Supplementary File 1 includes a comprehensive list of 363 PAAD-related pathways identified from the PAGER database, along with their scores from the ChatGPT-4o evaluation, which assessed their relevance to PAAD.

Supplementary File 2 details the scoring system and structured prompts provided to ChatGPT-4o, outlining the criteria and weights used to evaluate the pathways.

Supplementary File 3 presents the full rankings and scores of 129 PAAD-unrelated pathways, establishing a baseline for comparison against PAAD-related pathways.

Supplementary File 4 contains the complete list of ranked 252 candidate genes, prioritized using normalized Rank Prioritization Pathway (RPP) and Rank Prioritization Gene (RPG) scores.

Supplementary File 5 provides the results of a sensitivity analysis that examines pathway scores after adjusting the weight of the pathway relevance category by 10%, demonstrating the stability of the scoring framework.

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