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Role of Molecular-Genetic Profiling and Artificial Intelligence in Breast Cancer Diagnosis and insight into Targeted Pharmacotherapeutics

Srikanth Umakanthan, Arun Rabindra Katwaroo, Maryann Margaret Bukelo, Sreedhara Rao Gunakala, Alveera Dsouza, Maria Frances Bukelo, Vivek Shanker Adesh, Lexley Pinto Pereira, Parveen Kumar & Madan Mohan Gupta

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ABSTRACT

Breast cancer is a complex and diverse disease with varying responses to therapeutics. To address this diversity and offer personalized treatment plans, molecular and genetic analysis of breast tumors is crucial. The World Health Organization classifies breast cancer into different subtypes, including precursor lesions like Ductal carcinoma in-situ (DCIS), lobular carcinoma in-situ (LCIS), and Pleomorphic LCIS, which have the potential to develop into cancer. Invasive breast carcinomas infiltrate nearby tissues and can metastasize. These subtypes are categorized based on their microscopic appearances, such as Invasive Ductal Carcinoma (NOS), Invasive Lobular Carcinoma, Triple-Negative Breast Cancer (Estrogen receptor, Progesterone receptor, and, HER2), HER2-Positive Breast Cancer (HER2 overexpression), and less common types like Mucinous, Metaplastic, and Papillary carcinomas.

Keywords: genomics, sequencing, metastasis, prosigna, resistance, transduction.

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Role of Molecular-Genetic Profiling and Artificial Intelligence in Breast Cancer Diagnosis and insight into Targeted Pharmacotherapeutics

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ABSTRACT

Breast cancer is a complex and diverse disease with varying responses to therapeutics. To address this diversity and offer personalized treatment plans, molecular and genetic analysis of breast tumors is crucial. The World Health Organization classifies breast cancer into different subtypes, including precursor lesions like Ductal carcinoma in-situ (DCIS), lobular carcinoma in-situ (LCIS), and Pleomorphic LCIS, which have the potential to develop into cancer. Invasive breast carcinomas infiltrate nearby tissues and can metastasize. These subtypes are categorized based on their microscopic appearances, such as Invasive Ductal Carcinoma (NOS), Invasive Lobular Carcinoma, Triple-Negative Breast Cancer (Estrogen receptor, Progesterone receptor, and, HER2), HER2-Positive Breast Cancer (HER2 overexpression), and less common types like Mucinous, Metaplastic, and Papillary carcinomas. Molecular and genetic profiling are powerful tools to aid in treatment decisions. Understanding the underlying biology of the disease helps physicians develop personalized treatment plans that consider the unique characteristics of each patient's tumor. Ongoing advancements in technology and research are improving our ability to diagnose and treat breast cancer effectively. This review presents an insight into molecular genetic profile, the role of artificial intelligence in breast cancer, and a concise overview of targeted pharmacotherapeutics for treating hormone receptor-based breast cancer.

Keywords: genomics, sequencing, metastasis, prognosis, resistance, transduction.

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I. INTRODUCTION

Breast cancer, a historically enigmatic malignancy, is now being illuminated by powerful insights provided by molecular testing. This revolutionary approach has transformed the landscape of cancer diagnosis by delving deeper than traditional methods, enabling a thorough examination of the tumors' genetic and molecular makeup [1]. Such in-depth analysis can reveal the unique characteristics of each tumor, paving the way for targeted treatment, improved prognosis, and a ray of hope for cancer patients. The rapid transition from traditional radiology-based diagnostics to precise genetic

profiling of tumor suppressor genes has significantly expanded our understanding of breast cancer. It has led to classifying a broader spectrum of subtypes, each with distinct vulnerabilities and potential for targeted treatment [2]. This detailed understanding empowers medical professionals to develop highly tailored therapies to create a precise match between the treatment and the specific characteristics of each tumor. Molecular testing is also crucial in predicting the likelihood of cancer recurrence, guiding decisions about adjuvant therapy, and offering invaluable insights into overall prognosis [3]. Additionally, it catalyzes cutting-edge research, driving the development of novel treatments and strategies for personalized medicine. Through this continued progress in understanding the genetic and molecular underpinnings of breast cancer, a future is being shaped where tailored treatments and improved outcomes are within reach [4].

II. MOLECULAR AND GENETIC PROFILING

Breast cancer is a formidable and widespread threat that impacts millions of lives annually. It represents nearly a quarter of all new cancer diagnoses in women, underscoring the urgency of comprehending its developmental patterns and its impact on diverse demographic groups [5]. Developed nations display higher incidence rates due to aging populations and lifestyle choices. Nevertheless, even low- and middle-income countries are witnessing a surge in cases as their populations age and adopt Western behaviors [6]. The intricate nature of breast cancer is highlighted by an array of factors that influence an individual's susceptibility, including age, family history, genetic mutations, reproductive history, and lifestyle decisions. Specific lifestyle factors, such as obesity, alcohol consumption, and physical inactivity, can heighten the risk, besides contributory factors of early menarche, late menopause, and lack of breastfeeding. [7]. Early detection through regular screening, particularly in regions with limited resources, offers promise in intercepting the disease before it advances. Moreover, the evolving research landscape offers

encouraging treatment options, including targeted therapies, immunotherapy, and personalized medicine approaches that are pivotal in tailoring care for each case [8]. Appreciating the interplay between geographical factors, genetics, and lifestyles empowers us to reshape the narrative of breast cancer from a global shadow to a testament to resilience and prevention.

Molecular profiling thoroughly investigates different molecules within a tumor, such as DNA, RNA, and proteins. DNA analysis unveils genetic alterations, such as mutations, insertions, deletions, and rearrangements, contributing to cancer development and progression. RNA assessment provides insights into cellular processes and potential therapeutic targets by evaluating the expression levels of various genes. Analyzing protein expression and activity can aid in identifying biomarkers for diagnosis, prognosis, and treatment response [9,10]. Genetic profiling explores deep into the intricate analysis of DNA to unveil crucial details, such as mutations in genes associated with cancer, such as the BRCA1/2, TP53, and HER2 types, which significantly influence tumor aggressiveness and response to treatment. Additionally, alterations in chromosomal regions, known as copy number alterations, can impact gene expression and contribute to tumor development. Furthermore, merging different genes, known as gene rearrangements, can produce novel proteins that fuel cancer growth [11,12].

Molecular and genetic profiling has revolutionized the landscape of breast cancer management, enabling tumor classification into distinct subtypes [13]. These subtypes, such as luminal A, luminal B, HER2-enriched, and triple-negative breast cancer, exhibit unique clinical characteristics, prognosis, and responses to treatment depending on the immunoreactivity to estrogen receptors (ER), progesterone receptors (PR) and HER2 (Figure 1-3). Moreover, specific genetic alterations can serve as indicators of a higher risk of cancer recurrence, consequently influencing decisions regarding adjuvant therapy. Identifying mutations or gene expression patterns also facilitates the selection of targeted therapies that counter specific cancer-driving pathways.

Understanding the molecular underpinnings of developing innovative targeted therapies and breast cancer progression holds the promise of personalized treatment approaches [14].

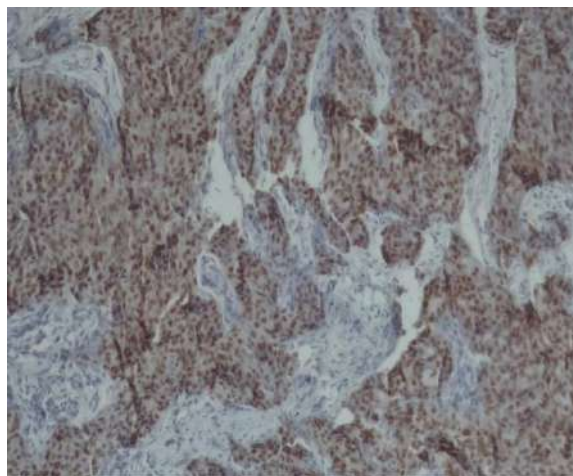


Figure 1: ER-Positive Tumor Cells (x40)

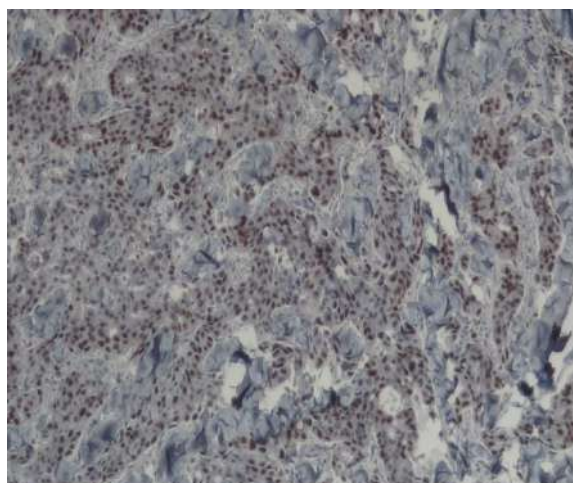


Figure 2: PR Positive Tumor Cells (x40)

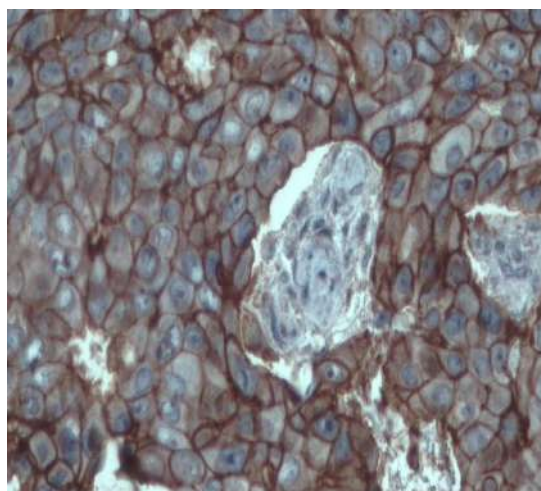


Figure 3: HER-2 Expressed as Strong Membrane Staining (3+)

Molecular testing in breast cancer has transcended the realm of futuristic possibilities and has become an essential component of present-day patient care. The advent of multigene assays has sparked a paradigm shift in the management of early-stage, hormone receptor-positive (HR+) breast cancer. Sophisticated tools such as Oncotype DX, MammaPrint, Prosigna, and Breast Cancer Index go beyond traditional clinicopathological parameters' constraints by meticulously analyzing multiple genes' collective expression patterns [15, 16]. This in-depth analysis, akin to deciphering the molecular blueprint of a tumor, yields a wealth of clinically actionable insights. For instance, the Oncotype DX test examines the expression of 70 genes to determine the likelihood of breast cancer recurrence and offers guidance on adjuvant therapy. Similarly, the MammaPrint test evaluates 70 genes to classify breast cancer into subtypes and predict the risk of recurrence. In addition, BRCA testing identifies mutations in the BRCA1 and BRCA2 genes, which may elevate the risk of developing breast and ovarian cancer [17,18].

2.1 Next-Generation Sequencing (NGS)

NGS provides a comprehensive view of a tumor's genetic alterations by examining its entire genome. NGS is ushering in an era of comprehensive genomic profiling and personalized medicine [19]. Unlike traditional targeted assays, NGS panels can simultaneously analyze thousands of genes, unraveling the intricate genetic landscape of tumors in unprecedented detail. NGS surpasses the limitations of single-gene analyses by revealing a broader spectrum of mutations and genomic alterations, including rare mutations, driver mutations in unconventional pathways, and complex chromosomal rearrangements. This capability has paved the way for identifying novel therapeutic targets, such as mutations in genes like ESR1 and ERBB2/HER2 amplifications, leading to targeted therapies like aromatase inhibitors and antibody-drug conjugates [20-22].

2.2 Guiding Clinical Trial Design

The comprehensive data generated by NGS panels is invaluable for stratifying patients for clinical

trials with targeted therapies or novel immunotherapy agents. By identifying specific genetic aberrations or molecular signatures associated with response, NGS can optimize clinical trial design and accelerate the development of personalized treatment options for patients with unique genomic profiles.

Tailoring Treatment Strategies: With a deep understanding of the tumor's genetic makeup, NGS empowers clinicians to develop personalized treatment plans beyond traditional clinicopathological parameters. This knowledge can guide the selection of targeted therapies, optimize chemotherapy regimens, and inform decisions regarding adjuvant therapy based on individual risk profiles [23]. For instance, identifying BRCA1/2 mutations may guide the use of PARP inhibitors, while ERBB2/HER2 amplifications may indicate the potential benefit of trastuzumab-based therapy [24].

2.3 Unlocking Novel Therapeutic Targets

The ever-expanding library of mutations and alterations detected by NGS fuels the discovery of novel therapeutic targets. NGS paves the way for developing new drugs and targeted therapies for specific molecular pathways in breast cancer by identifying actionable genomic aberrations [25]. This ongoing research holds immense promise for expanding the armamentarium of available treatments and improving outcomes for patients with diverse genomic profiles [26]. To make the most of NGS for managing breast cancer, it's essential to overcome certain obstacles. Interpreting and integrating data from NGS generates large amounts of complex information requiring robust computational tools and algorithms to analyze and integrate clinical factors accurately. [27].

2.4 The Changing Tumor Environment

Tumor heterogeneity demands dynamic profiling techniques that account for the evolution of the genomic landscape and adjust treatment strategies accordingly. One of the most compelling applications of multigene profiling lies in its ability to predict the risk of cancer

recurrence [28]. By meticulously quantifying the expression of genes associated with cell proliferation, invasion, and drug resistance, these assays provide a nuanced assessment of future disease dissemination. This information empowers clinicians to stratify patients into distinct risk categories, optimizing adjuvant therapy decisions. For patients classified as low risk based on multigene profiling, the potential benefits of chemotherapy may be outweighed by the associated toxicities, allowing for treatment de-escalation and improved quality of life. Conversely, for patients classified as high-risk, more aggressive adjuvant regimens can be tailored to combat the heightened threat of recurrence effectively [29].

Furthermore, multigene assays possess the unique ability to predict the potential benefit of chemotherapy in individual patients. By comprehensively evaluating the interplay between tumor genomic expression and clinical characteristics, these tests can identify patients unlikely to experience a significant survival advantage from chemotherapy. This personalized approach spares patients from unnecessary toxicities and significantly reduces healthcare costs [30,31]. The clinical significance of multigene profiling goes beyond merely identifying the risk and predicting treatment outcomes. These assessments provide valuable insights into the classification of tumor subtypes, further refining our comprehension of breast cancer heterogeneity [32, 33]. By investigating into the molecular foundations of each tumor, multigene profiling can pinpoint subtle differences within traditional subtypes, such as luminal A and B. This enhanced level of detail enables the development of more targeted treatment plans tailored to the unique molecular profile of each tumor. Multigene profiling has become a fundamental aspect of personalized medicine in early-stage HR+ breast cancer. By meticulously examining the molecular landscape of the tumor, these assessments empower clinicians to make evidence-based treatment decisions, optimize clinical outcomes, and minimize unnecessary therapeutic burden. As our understanding of tumor biology and multigene

data analyses continues to evolve, we can anticipate further enhancements to these powerful tools, ultimately leading to a future of truly personalized cancer care [34].

2.5 Utilizing Molecular Sequencing

Ductal carcinoma in situ (DCIS), a non-invasive precursor to invasive breast cancer, presents a challenging clinical dilemma. While it is not an immediate threat, DCIS has the potential to progress to invasive disease [35]. This brings up the critical question: How do we navigate the treatment options for DCIS, balancing the potential benefits of aggressive treatment against the risk of overtreating low-risk cases? This is where Oncotype DX DCIS and DCISionRT, two advanced molecular assays, emerge as invaluable tools for guiding the way forward. These assays surpass the limitations of traditional clinicopathological factors by deeply into the molecular mechanisms of the tumor [36]. A rigorous analysis of the expression patterns of multiple genes associated with cell proliferation, invasion, and resistance to therapy provides a detailed and personalized risk assessment for the recurrence of DCIS. This prognostic information forms the cornerstone of treatment decision-making for patients diagnosed with DCIS [37].

Oncotype DX DCIS primarily focuses on stratifying the risk of recurrence. Categorizing patients into distinct risk groups (low, intermediate, or high) provides crucial guidance on the necessity of adjuvant radiation therapy. For patients identified as low risk by the test, radiation therapy can be safely omitted, sparing them from unnecessary side effects and potential psychological distress [38]. Conversely, Oncotype DX DCIS is a valuable tool for optimizing treatment strategies for high-risk patients. It may reveal the need for more aggressive approaches, such as additional surgery or more intensive radiation regimens, to effectively mitigate the elevated risk of recurrence. DCISionRT, however, goes beyond mere risk stratification [39]. It can uniquely predict the potential benefit of adjuvant radiation therapy. By considering both the inherent aggressiveness of the tumor, as revealed by gene expression, and the specific clinical

characteristics of the patient, DCISionRT identifies patients who are unlikely to experience a significant survival advantage from radiation. This personalized approach enables clinicians to tailor treatment plans for each individual and reduce healthcare costs by eliminating unnecessary interventions. Furthermore, Oncotype DX DCIS and DCISionRT can contribute to refining tumor classification. By providing insights into the underlying molecular landscape of DCIS, these assays help identify subtle variations within traditional subtypes, potentially informing the development of more precise and targeted treatment strategies [40-42].

The field of genomic tools in the context of early-stage breast cancer is constantly evolving, with novel companion diagnostics taking center stage in personalized medicine. While multigene assays such as Oncotype DX and MammaPrint have excelled in prognosis and treatment de-escalation, the emergence of companion diagnostics designed to guide targeted therapies represents a significant shift in cancer care [43]. A prime example of this shift is the identification of PIK3CA mutations, which are present in around 20% of breast cancers, particularly in those classified as luminal HR+. These mutations are associated with aggressive tumor behavior and resistance to standard therapies [44]. However, the development of PIK3CA inhibitors like alpelisib and buparlisib offers hope. Companion diagnostics designed to detect PIK3CA mutations enable identifying patients who can significantly benefit from these targeted therapies, paving the way for a more precise and effective treatment approach [45].

Similarly, NTRK fusions, though rare in breast cancer, represent another actionable target. These gene rearrangements produce a chimeric protein with oncogenic properties, driving tumor growth and progression. Precision drugs like entrectinib have shown remarkable efficacy in targeting NTRK fusions across various tumor types, including breast cancer. The role of companion diagnostics is crucial in identifying patients harboring these rare alterations, offering them access to transformative targeted therapies that were previously unimaginable [46].

The implications of companion diagnostics extend beyond individual success stories. This approach could optimize resource allocation by directing targeted therapies toward patients most likely to respond. This approach could minimize unnecessary exposure to ineffective treatments and related costs while potentially leading to superior response rates and progression-free survival compared to conventional therapy. Additionally, patients benefit from companion diagnostics by gaining insight into their tumor's genomic profile and potential treatment options, allowing them to engage in informed discussions about their care and fostering a sense of agency and autonomy [47]. Unlike traditional therapies, which directly target tumor cells, immunotherapy engages the immune system to recognize and eliminate cancerous cells. To navigate this new frontier, specialized assays have been developed to guide patient selection and predict treatment responses in a personalized manner [48].

One significant element in this evolving scenario is PD-L1 expression analysis. PD-L1, a protein expressed on both tumor cells and immune cells, acts as an immunosuppressive checkpoint molecule, hindering the antitumor activity of T cells. Immunohistochemistry assays employing specific antibodies quantify PD-L1 expression on tumor cells. Patients with high PD-L1 expression are considered potential candidates for anti-PD-L1 therapy, which activates the T cell response and unleashes their ability to combat the tumor [49]. This personalized approach, guided by PD-L1 expression testing, optimizes treatment efficacy while reducing exposure to ineffective therapies. The significance of various tumor-intrinsic markers in identifying the immunological vulnerability of tumors, mainly focusing on markers such as PD-L1 expression, microsatellite instability (MSI), mismatch repair deficiency (MMRd), and tumor mutational burden (TMB). These markers serve as valuable indicators of a pre-existing antitumor immune response, suggesting their potential to predict the responsiveness of tumors to immunotherapy [50-53]. Moreover, the text emphasizes the clinical implications of incorporating these immunological markers, such as improved patient

selection and enhanced treatment monitoring, as well as the challenges associated with fully leveraging the potential of these emerging assays, including the need for standardization of testing protocols and interpretation criteria [54].

III. DRAWBACKS OF MULTIGENE ASSAYS

In breast cancer treatment, multigene assays provide clinicians with a diverse array of tools to help make informed treatment decisions. However, each assay has its own set of unique strengths and limitations, making it crucial for clinicians to have a distinct understanding of their capabilities to select the most appropriate assay for their patients. The four prominent multigene assays: Oncotype DX, MammaPrint, Prosigna, and Breast Cancer Index.

3.1 Oncotype DX

Widely recognized and validated, this assay predicts prognosis and determines whether treatment can be scaled down. It focuses on proliferation genes and hormone receptor activity, enabling accurate risk stratification for early-stage, hormone receptor-positive breast cancer [57]. For patients identified as low risk by Oncotype DX, the potential benefits of chemotherapy may not outweigh the associated side effects, empowering clinicians to spare them from unnecessary treatment confidently. However, it may only partially capture the aggressive potential of tumors driven by pathways other than proliferation [58].

3.2 Mamma Print

Unlike Oncotype DX, MammaPrint emphasizes analyzing genes associated with epithelial-mesenchymal transition and extracellular matrix remodeling to assess invasion and tumor aggressiveness. This makes MammaPrint particularly sensitive in identifying high-risk tumors that may benefit from more aggressive therapeutic approaches. However, its focus on proliferation may overlook low-risk tumors suitable for less aggressive treatment [59].

3.3 Prosigna

Taking a holistic approach, Prosigna integrates gene expression analysis with clinical factors such as tumor size, nodal involvement, and age. This comprehensive perspective results in a multifaceted risk assessment, providing valuable insights beyond proliferation or invasion. Prosigna's strength lies in its ability to cater to a broader range of patients, including those with triple-negative or HER2-positive tumors, where other assays may offer limited information [60]. However, its complexity makes careful interpretation and integration with clinical context essential.

3.4 Breast Cancer Index (BCI)

Focusing on a specific niche, BCI utilizes a unique algorithm to predict the likelihood of response to endocrine therapy [61]. This provides valuable information for tailoring treatment plans for patients with hormone receptor-positive tumors. However, BCI's predictive power primarily lies in this context, limiting its applicability in other scenarios [62].

Selecting the most suitable assay involves evaluating various factors, including tumor characteristics (subtype, stage, hormone receptor status), patient preferences, and physician expertise. Ultimately, the optimal multigene assay selection is a collaborative decision between the clinician and patient, considering the individual benefits and limitations of each tool, the specific clinical context, and patient preferences (Figure 4). As research continues to improve existing assays and introduce new ones, clinicians must stay abreast of developments to ensure patients receive the most precise and personalized care available.

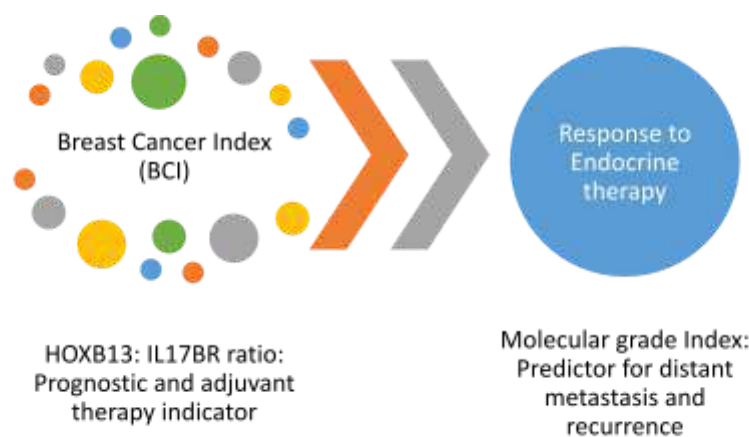


Figure 4: " Breast Cancer Index Rationale

IV. LEVERAGING ARTIFICIAL INTELLIGENCE (AI) FOR BREAKTHROUGHS IN BREAST CANCER MOLECULAR GENETICS

Artificial intelligence (AI) has emerged as a transformative and formidable influence in shaping clinical diagnosis, drug discovery, and patient care in the contemporary medical landscape. AI systems possess the remarkable ability to analyze vast datasets of medical records, radiological and histological images, and genomic data stored within healthcare institutions. They present crucial insights that empower us to recognize, quantify, and correlate complex patterns within data. Implementing AI-driven analysis fosters more accurate and personalized patient diagnoses, informs research initiatives for novel drug therapies, and facilitates the development of effective, multidisciplinary treatment plans for chronic diseases [63].

Medical imaging has exceptional potential within the spectrum of promising AI applications in modern medicine. AI-powered algorithms are now being developed to achieve superior accuracy and sensitivity in identifying cancerous cells and other lesions within medical images. This technical advance is promising for early diagnosis and treatment intervention, with beneficial patient outcomes [64]. Breast cancer research is a field that can profit immensely from the integration of AI-powered molecular analysis. By harnessing the power of AI to analyze vast quantities of genetic data, researchers can gain

deeper insights into the complex mechanisms that initiate breast cancer and sustain its progress. Such knowledge is foundational to developing targeted therapeutics that are precision zeroed in on breast cancer cells [65].

Though imaging modalities have been pivotal in the early detection and clinical staging of breast cancer, they present challenges in clinical practice. The burgeoning volume of imaging data generated during breast cancer diagnosis inflicts a significant work burden on radiologists. Further quality limitations and ambiguity of imaging can compromise diagnostic accuracy. Moreover, the subtle complexity of the disease presentations often necessitates combined imaging and clinical data analysis for comprehensive evaluation [63,64].

Radiologists now use computer-aided diagnosis (CAD) as an efficient tool to interpret medical images and highlight and evaluate noticeable/suspicious lesions to support accurate clinical diagnoses and decisions. As an early form of AI, advancements in CAD led to the development of more flexible and versatile analyses, particularly image-based artificial intelligence (AI) techniques. These AI-powered methods significantly augment the clinical value of CAD in breast cancer diagnosis [65].

Reliable CAD methods coupled with high-performance computing are crucial to ensure accurate diagnoses. The underlying computational techniques directly influence the accuracy of interpretation of these systems. Therefore, optimizing the performance of AI-based breast

cancer screening and diagnosis is paramount in effectively supporting radiologists' work [66].

Radiology and pathology are witnessing a paradigm shift with the introduction of digital workflows and AI. The expansile era of precision medicine demands decidedly accurate and comprehensive diagnostic tests. The emergence of digital imaging and Picture Archiving and Communication Systems (PACS), along with whole slide images (WSI) and digital pathology, has significantly reshaped diagnostic medicine, with the emergence of a merged single novel entity of the "information specialist" as a suggested new role for pathologists and radiologists [67].

AI systems have remarkably developed over the past two decades, progressing from machine learning (ML) to deep learning (DL) to transformer models capable of integrating multimodal data as inputs. Convolutional Neural Networks (CNNs) represent a famous DL image-analysis architecture [64,66]. Their ability to extract spatial and contextual information from images through multiple convolutional layers offers a significant advantage. When trained on comprehensive, labeled datasets, CNNs can perform tasks such as segmentation, prediction, and detection with exceptional accuracy and efficiency. Transfer learning, a valuable DL technique, establishes foundational capabilities for image-related tasks. By leveraging pre-trained models developed using large datasets, transfer learning facilitates the transfer of learned features and representations to new tasks with limited labeled data. This approach improves performance and reduces the need for extensive training from scratch [66,67].

AI systems have demonstrated superior performance to human experts in predicting long-term breast cancer risk and patient prognosis. In breast pathology, AI algorithms have successfully been implemented for various tasks, including cancer detection, classification, histologic grading, lymph node (LN) metastasis detection, biomarker quantification, and even the prediction of genetic abnormalities such as BRCA mutations [63,65].

While computer-aided diagnosis (CAD) systems have found widespread application in mammography, conventional programs relying on prompts to highlight potential lesions have yet to improve diagnostic accuracy demonstrably. Innovations in machine learning, particularly the emergence of deep learning architectures like multilayered convolutional neural networks (CNNs), have significantly transformed the field of artificial intelligence (AI). These advancements have led to noteworthy upgrades in the predictive capabilities of AI models [67]. Deep learning algorithms have been successfully applied to mammography and digital breast tomosynthesis (DBT) in recent years [68].

Current deep learning algorithms exhibit promising performance, approaching the level of human radiologists in cancer detection and risk prediction within mammography. Nevertheless, these fruitions could be improved by a need for robust clinical validation. Consequently, the optimal integration of deep learning's potential to optimize clinical practice remains to be determined. Further development of deep learning models tailored explicitly for DBT analysis is essential, calling for the collection of vastly extensive and comprehensive databases to facilitate practical training [68]. Despite these limitations, deep learning is anticipated to play a pivotal role in the future of DBT, with applications potentially extending to the generation of synthetic images [69].

V. IDENTIFYING GENETIC DRIVERS OF BREAST CANCER

AI can analyze large datasets of genetic mutations to identify patterns and correlations. Researchers can thus pinpoint specific genes or combinations of genes that program breast cancer development-crucial knowledge to develop targeted therapies. Oncology has entered uncharted waters where the integration of medical imaging and genomics, facilitated by the transformative power of AI, has significant potential for rapid and accurate evaluation of a patient's tumor genetic status. Researchers are actively exploring the development of radiometric signatures (Figure 5). These AI-derived signatures, based on the

analysis of data from imaging modalities such as computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), mammography, and digital tomosynthesis, hold promise for the non-invasive prediction of genetic alterations within tumors [63,65,67]. Furthermore, these AI-enabled macro-level imaging biomarkers can be leveraged to assess treatment response and patient prognosis. Notably, some AI-powered tools have demonstrated diagnostic performance comparable to or surpassing that of human

experts. Within the domain of pathology, the gold standard for genetic testing, AI is seen as a valuable tool to augment the efficiency of pathologists in interpreting complex molecular profiles. Therapeutic approaches could be highly personalized for breast cancer patients. Several challenges, though, remain to be addressed, such as the widespread clinical adoption of AI-powered tools in the field. Critical evaluation and attention to these challenges will ultimately allow the potential of this transformative technology to be achieved [68,69].

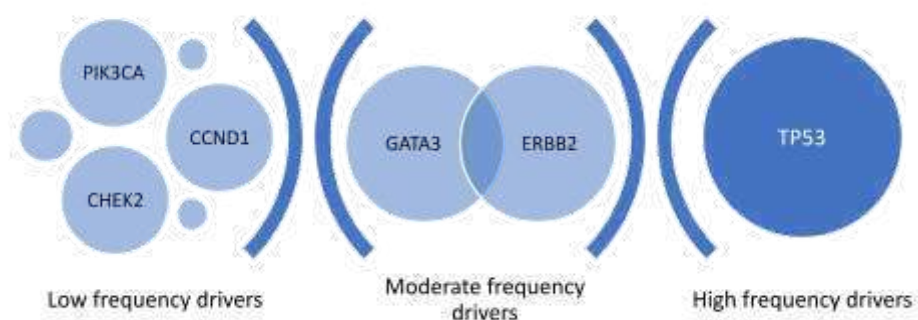


Figure 5: Genetic Drivers of Breast Cancer Based on Frequency and Intensity

Oncologists have long envisioned AI's transformative potential in delivering highly personalized cancer care. This vision is steadily materializing due to a confluence of scientific developments. These include the continued refinement of machine learning (ML) and deep learning (DL) algorithms, the exponential growth and diversification of healthcare databases, including multi-omics data, and the declining cost of massively parallelized computing power [62,65]. Within AI, two primary paradigms guide model development: symbolic AI (SAI) and data-driven AI (DAI). Symbolic AI, grounded in human expertise, utilizes human-readable symbols and "if-then" rules to arrive at conclusions. This approach is particularly suited for deterministic situations where explicit knowledge encoding is effective [64]. SAI empowers them to reason and reach informed judgments by incorporating human knowledge and rules into computer systems. In essence, SAI leverages pre-defined regulations to arrive at conclusions, requiring minimal to no learning from data (Figure 6).

In contrast, the data-driven AI paradigm draws upon historical data as a form of experience. This data is used to develop mathematical equations that generate intelligent decisions. The informed AI (IAI) concept bridges the gap between SAI and DAI approaches. IAI integrates human-domain expertise into the model development process to create the target variable (i.e., data annotation) and enhance model interpretability [70]. Data-driven AI plays a pivotal role in cancer research. However, ensuring data security and privacy while performing inferences from encrypted data presents a challenge. Protopia AI's Stained-Glass Transforms offer a promising solution by mitigating the risk of sensitive data leakage during analysis. These transformations are compatible with various formats, including tabular data, text, images, and videos [71].

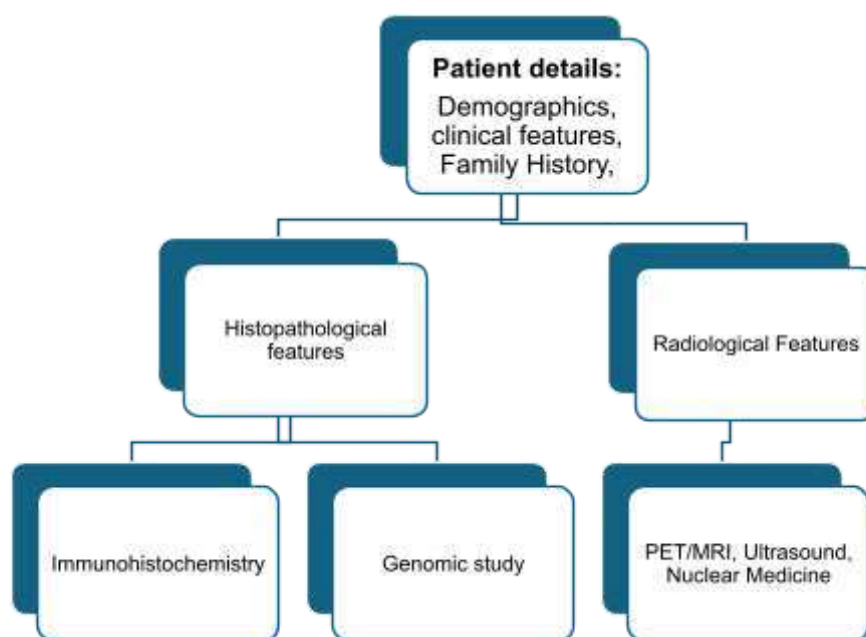


Figure 6: Algorithm in Data-Driven AI Paradigm

The availability of open-source healthcare data has empowered researchers to develop cancer identification and prognosis tools. Machine learning and deep learning models offer reliable, rapid, and efficient solutions for addressing challenges in cancer treatment, mainly when applied to distributed datasets. Federated learning models represent an advanced approach to distributed data analysis. Several emerging techniques are promising for clinical applications: whole-blood, multi-cancer detection using deep sequencing, virtual biopsies, Natural Language Processing (NLP) for inferring health trajectories from medical records, and advanced clinical decision support systems integrating genomics and clinomics data [72,73].

Oncology has traditionally relied on evidence-based medicine scoring systems for various aspects of cancer management, including risk assessment, diagnosis, prognostication, treatment selection, and surveillance. These systems have evolved from basic light microscopy observations to more sophisticated techniques like gene expression profiling and next-generation sequencing of somatic and germline genomes. AI is further opening doors to exploring synergistic drug combinations for cancer treatment [64]. In breast cancer, AI straddles the arenas of screening, diagnosis, tumor staging, treatment, and follow-up, encompassing response status

disease progression and relapse [65]. AI is revolutionizing breast cancer research by offering powerful tools to analyze complex genetic data and translate those findings into actionable insights for patient care. One key area of impact lies in risk stratification. AI algorithms can analyze a patient's genetic profile alongside other clinical factors to predict their risk of developing breast cancer. This information empowers healthcare professionals to implement personalized prevention strategies, such as increased screening for high-risk individuals [62,67].

Furthermore, AI is transforming the landscape of drug discovery and development. By analyzing vast libraries of molecules and patient data, AI can identify potential drug targets and predict the effectiveness of existing or newly developed therapies. This significantly accelerates the drug discovery process, paving the way for more effective treatments to reach patients sooner. Understanding tumor heterogeneity is another crucial aspect of breast cancer research. Breast tumors often exhibit genetic heterogeneity, meaning different tumor parts may harbor distinct mutations. AI's ability to analyze this complex data provides valuable insights into how these mutations interact and contribute to tumor progression. This knowledge is instrumental in developing more effective treatment strategies

targeting the specific mutations within each patient's tumor [65,69].

Finally, AI plays a vital role in analyzing gene expression. AI can analyze the expression levels of thousands of genes within a tumor sample. This information helps researchers understand the biological pathways involved in cancer development and identify potential biomarkers [74]. These biomarkers can be used for more accurate diagnosis and personalized treatment selection, ultimately improving patient outcomes.

VI. TARGETED PHARMACOTHERAPEUTICS

Most breast cancers, around 90%, test positive for estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) proto-oncogene. Targeted treatments for these receptors have improved survival rates, but resistance to these treatments is common, leading to cancer recurrence or progression. The remaining 10% of breast cancers do not have these receptors (triple-negative), and there are no established targeted drugs for this group yet. Therefore, finding new targeted therapies for triple-negative breast cancer is a crucial challenge. Preclinical studies on the mechanisms of resistance to standard therapies have identified promising targets, including mTOR Inhibitors, PI3K inhibitors, TKIs, monoclonal antibodies, and Immune Checkpoint Inhibitors.

6.1 Mtor Inhibitors: These Include Everolimus, Temsirolimus and Sirolimus

Everolimus is used in postmenopausal women with ER-positive and HER2-negative metastatic breast cancer that is resistant to aromatase inhibitors. It is taken in combination with endocrine therapy to improve progression-free survival. Everolimus works as an oral inhibitor of rapamycin and is generally well-tolerated. Common side effects include fatigue, rash, stomatitis, hyperlipidemia, hyperglycemia, myelosuppression, and non-infectious pneumonitis. Adjusting or reducing the dosage can resolve most of these side effects. It's

important to be alert to the drug's dose-related toxicity to allow timely interventions.

The BOLERO-2 study added everolimus to exemestane, significantly improving progression-free survival rates for patients. There was a 57% reduction in hazard ratio, with observed medians of 6.9 months for everolimus plus exemestane compared to 2.8 months for exemestane alone. These results were confirmed through an independent, blinded radiologic assessment and were consistent across all subgroups [77]. Another study involving neoadjuvant everolimus with letrozole in patients with newly diagnosed breast cancer showed reduced tumor-cell proliferation and improved clinical response rates compared to letrozole treatment alone [78]. In a recent randomized, phase 2 study of 111 postmenopausal women with ER-positive advanced breast cancer who were previously treated with an aromatase inhibitor, the combination of everolimus and tamoxifen was associated with significantly improved progression-free survival compared to tamoxifen alone (8.6 months vs. 4.5 months, $P=0.002$) and improved overall survival (median not reached vs. 24.4 months, $P=0.01$). Based on the data from these studies, everolimus seems to enhance the anticancer activity of antiestrogen therapy across various clinical settings for breast cancer patients [79].

Temsirolimus (TEM) functions by inhibiting the phosphorylation of mTOR within cancer cells, promoting autophagy in the targeted cancer cells. Furthermore, TEM serves as an antifungal agent by enhancing the solubility of water-soluble rapamycin and addressing its low pharmacokinetic properties. mTOR is crucial in regulating cancer cell response to growth factors, survival, and proliferation. In breast cancer cells, upregulated mTOR activity accelerates tumorigenesis and angiogenesis and inhibits autophagy [80]. This effect has also been observed in patients with renal cell carcinoma, contributing to improved prognosis and 10-year survival rates. According to recent studies, TEM has shown enhanced anti-tumoral activity in various cancers, including medulloblastoma, neuroectodermal tumors, and pancreatic carcinomas. Park SS et al. found that TEM

suppresses tumors in breast cancer cells and enhances CD8+ T cell-mediated anti-cancer effects by reducing levels of PD-L1 in breast cancer-derived sEV. Furthermore, combining TEM and anti-PD-L1 increased the number and activity of CD4+ and CD8+ T cells in tumors and Distant Lymph Nodes of immunocompetent mice with breast cancer. This suggests that TEM, previously used as a targeted anti-cancer drug, can potentially be developed as a new anti-cancer therapy that can effectively enhance cancer treatment by suppressing sEV PD-L1 secretion and improving the immune system in the body.

The drug TEM was found to have a documented objective response rate of 9.2% and a median time to tumor progression of 12 weeks. In heavily pretreated patients with locally advanced or metastatic breast cancer, both 75 mg and 250 mg temsirolimus showed antitumor activity, while the 75 mg dose also exhibited a generally tolerable safety profile [84]. The drug's efficacy was consistent across low and high doses, but drug toxicity was more common at higher doses. The adverse effects of TEM, based on frequency, included grade 4 depression (10% of patients at the 250-mg dose level, 0% at the 75-mg dose level), mucositis (70%), maculopapular rash (51%), nausea (43%), leukopenia (7%), hyperglycemia (7%), somnolence (6%), thrombocytopenia (5%), and depression (5%) [85].

Sirolimus, a specific mTOR antagonist, targets the PI3K/Akt/mTOR pathway and inhibits downstream signaling elements. When administered at low doses (2 mg/day) for short-term (5–7 days) treatment, sirolimus has been shown to significantly reduce p16INK4A, COX-2, and Ki67, which are predictive biomarkers of breast cancer progression. Early-phase clinical studies have explored its safety in breast cancer patients, and its tolerability makes it an attractive alternative to everolimus. However, the effectiveness of sirolimus in HR-positive advanced breast cancer remains uncertain and requires further investigation in breast cancer patients. Reported adverse reactions to sirolimus in past studies vary significantly depending on disease progression and treatment duration [86].

In advanced cancer patients, sirolimus has been associated with hyperglycemia, hyperlipidemia, lymphopenia, anemia, and diarrhea as the most common adverse effects. The spectrum of adverse effects of sirolimus differs from that observed with everolimus. Other common adverse effects include fatigue, leukopenia, neutropenia, and increased ALT or AST levels. A study conducted by Yi et al. indicated that the toxicity of 2 mg/day sirolimus was tolerable for advanced breast cancer patients [87]. However, these adverse effects may be underestimated in retrospective studies, and further validation through prospective randomized clinical studies is necessary.

6.2 PI3K inhibitors: These include Alpelisib, Taselisib, and Pictilisib

Alpelisib- The proliferation, differentiation, and survival of cancer cells are mainly determined by the PI3K/AKT/mTOR pathway. The breast cancer cells frequently harbor based on PIK3CA gene alterations, constituting an essential site for targeted drug therapy. However, it has engaged in many clinical trials globally to demonstrate this activity and attain regulatory approval from the FDA. Patients diagnosed with PIK3CA-mutated type of breast cancers benefit from PI3K inhibitor therapy. Alpelisib selectively inhibits PIK3 in the PI3K/AKT kinase signaling pathway, inhibiting the activation of the PI3K signaling pathway [88]. Alpelisib has better drug tolerance compared to other PI3K inhibitors. The common adverse effects include rash, hyperglycemia, and diarrhea that can be regulated and curtailed by intensive drug monitoring and timely intervention, allowing breast cancer patients to adhere to and extract the beneficial effects of the drug clinically. Based on the literature studies, alpelisib, in conjunction with endocrine therapy, has shown favorable drug efficacy for treating postmenopausal advanced breast cancer patients with ER+, PR+, and HER2-receptor status [89].

Alpelisib has shown better drug efficacy in breast cancer patients after disease progression who are on first-line endocrine therapy with or without combining with CDK4/6 inhibitors. PIK3CA mutation testing can be done upon diagnosing

ER+, PR+, and HER2-advanced breast cancer by utilizing either the circulating DNA from the tumor cells or the tumor tissue. Alpelisib has been of potential benefit to all eligible patients following pertinent drug toxicity management and careful patient selection [90]. Alpelisib has been assessed for fruitful combinations of hormone therapy with mTOR, PI3K, AKT, and CD4/6 inhibitors in other histological subtypes of breast cancer in women and men.

Taselisib is a potent PI3K inhibitor used in patients with PIK3CA-mutated advanced breast cancer. When combined with endocrine therapy, it has been proven to improve prognosis. The SANDPIPER trial analyzed circulating tumor DNA (ctDNA) from PIK3CA or PIK3CA mutated breast cancer patients. The study found no detectable mutations in baseline ctDNA [91]. Tumor fraction estimates, and top mutated genes were further analyzed for their association and outcomes. In patients with PIK3CA mutated breast cancer, ctDNA treated with a combination of taselisib + fulvestrant showed shorter progression-free survival when tumor suppressor gene protein p53 and fibroblast growth factor receptor-1 alterations were identified within the tumor cells, compared to patients with Nonsense-mediated mRNA decay in their genes. Conversely, in patients with PIK3CA mutated breast cancer, ctDNA revealed harboring a neurofibromin 1 (NF1) alteration with a high baseline tumor fraction estimate showed an improved tumor response when treated with a combination of taselisib and fulvestrant compared to fulvestrant and placebo combination [92].

Overall, changes in estrogen receptor (ER), PI3K, and p53 pathway genes were linked to resistance to the combination of taselisib and fulvestrant in individuals with PIK3CA mutation in circulating tumor DNA. In summary, the study has shown the influence of genetic alterations on outcomes using a sizable clinical-genomic dataset of patients with ER-positive, HER2-negative, and PIK3CA-mutated breast cancer treated with a PI3K inhibitor [93].

Pictilisib Approximately 40% of hormone receptor-positive, HER2-negative breast cancers

are linked to activating mutations of the PI3K pathway. Pictilisib, a specific and robust class I pan-PI3K inhibitor, has shown preclinical activity in breast cancer cell lines. It can enhance taxanes' effectiveness, benefiting patients regardless of their PI3K pathway activation status. Preclinical data indicates that the PI3K pathway plays a vital role in estrogen receptor-positive breast cancer. Combining PI3K inhibitors with endocrine therapy may help in overcoming resistance [94].

A preoperative study was conducted to determine if adding the PI3K inhibitor pictilisib could enhance the antitumor effects of anastrozole in primary breast cancer. The study aimed to identify the most suitable patient population for combination therapy. Pictilisib is a potent and selective pan-inhibitor of class I PI3K family members that can be taken orally, and it inhibits the p110 α , p110 β , p110 δ , and p110 γ subunits of PI3K. It binds to the adenosine triphosphate (ATP)-binding pocket of PI3K, preventing the formation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), a key signaling intermediary downstream of PI3K. In a phase I open-label dose-escalation study involving patients with advanced solid tumors, pictilisib demonstrated anti-tumor activity, on-target pharmacodynamic activity, and an acceptable safety profile at doses of ≥ 100 mg [95].

In the OPPORTUNE study trial, the addition of pictilisib to anastrozole in patients with preoperative early breast cancer showed a significantly increased anti-proliferative response compared with anastrozole alone. Moreover, the combination of pictilisib with weekly paclitaxel was well tolerated and demonstrated effective anti-tumoral activity in breast cancer patients. This document also reports the results of a phase II trial, which evaluated the addition of pictilisib to paclitaxel compared with paclitaxel plus placebo in treating patients with locally recurrent or metastatic HER2-negative, hormone receptor-positive breast cancer [96].

6.3 TKIs: include Lapatinib, Neratinib and Tucatinib

Lapatinib is a tyrosine kinase inhibitor (TKI) that competes with intracellular ATP to block the HER2 signal, thereby preventing phosphorylation and downstream changes in molecular pathways. Due to its unique mechanisms compared to monoclonal antibodies, lapatinib has an advantage in overcoming drug resistance [97]. In an Alternative III clinical study, patients treated with lapatinib + trastuzumab + aromatase inhibitors (AIs) experienced significantly longer median progression-free survival (PFS) than those treated with AI and trastuzumab. Furthermore, patients treated with AI and lapatinib had a longer median PFS than those treated with trastuzumab + AI (8.3 months vs. 5.6 months). However, in the ALLTO trial, trastuzumab was more effective than lapatinib. The combination of lapatinib with trastuzumab therapy has been reported to be more effective than trastuzumab therapy alone. The CHER-Lob and TRIO-US B07 trials showed that trastuzumab plus lapatinib treatment results in a better pathologic complete response outcome.

Additionally, ALTTO showed that in disease-free survival, there were no significant differences among the lapatinib plus trastuzumab, trastuzumab, and lapatinib therapy groups, although the combination group exhibited higher toxicity. Hence, it has yet to be conclusively determined whether the efficacy of trastuzumab plus lapatinib or lapatinib therapy is equal to trastuzumab therapy [98].

Neratinib is a small molecule that works as an irreversible inhibitor of HER1/2/4. It binds to the tyrosine kinase domain and blocks its interaction with adenosine triphosphate (ATP), stopping receptor phosphorylation. Neratinib can reverse multidrug resistance by affecting ATP-binding cassette (ABC) transporters. It disrupts the activity of ligand-phosphorylated HER2 and EGFR and inhibits downstream signaling of the Mitogen-activated protein kinase (MAPK) and AKT pathways. The primary pathways it affects include the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR pathways, which regulate cell

proliferation and apoptosis. Additionally, Neratinib can downregulate the expressions of other RTKs and mutant RAS proteins. It effectively inhibits the proliferation of EGFR- and HER2-expressing cell lines, leading to G1-to-S-phase cell cycle arrest and apoptosis. Positive human epidermal growth factor receptor 2 (HER2) expression is associated with an increased risk of metastases, particularly to the brain, in patients with advanced breast cancer [99].

Neratinib, a type of tyrosine kinase inhibitor, can disrupt the transmission of HER1, HER2, and HER4 signaling pathways, showing an anti-cancer effect. Additionally, Neratinib has been effective in reversing drug resistance in breast cancer patients who have previously shown resistance to HER2 monoclonal antibodies or targeted drugs. It has been tested in various scenarios, including neoadjuvant, adjuvant, and metastatic settings, alone and in combination with other treatments. Neratinib, known for its anti-cancer solid activity, is recommended for extended adjuvant treatment of HER2-positive early breast cancer. It is also used in combination with other drugs such as trastuzumab, capecitabine, and paclitaxel for the treatment of advanced HER2-positive breast cancer, particularly in cases with central nervous system (CNS) metastasis to lower the risk of breast cancer recurrence. The most common side effect of neratinib was gastrointestinal toxicity, primarily diarrhea. In breast cancer patients, the response rate to neratinib was $\geq 32\%$, and it was even higher when combined with other anti-HER2 agents (e.g., 63% when combined with T-DM1). Phase 1 data laid the groundwork for subsequent phase 2 studies to determine the effectiveness and safety of neratinib-based regimens more accurately. The maximum tolerated dose (MTD) of neratinib in phase 1 studies was 320 mg/day, but further clinical experience indicated unacceptable rates of diarrhea. Therefore, for the Phase 2 studies, a 240 mg/day dose was used as monotherapy [100].

Tucatinib is a highly selective small molecule inhibitor of the HER2 tyrosine kinase that has shown significant clinical benefits in advanced settings. It has demonstrated a remarkable

1000-fold increase in potency for HER2 inhibition compared to the estimated glomerular filtration rate. Furthermore, tucatinib has shown minimal induction of estimated glomerular filtration rate-related toxicities when used in combination-type studies. Importantly, it has proven effective in treating brain metastases, a significant challenge in advanced disease. The recent HER2CLIMB trial reported a 46% improvement in 12-month progression-free survival and a substantial increase in the objective response rate when tucatinib was combined with trastuzumab and capecitabine, compared to placebo. Although the combination of tucatinib and immunotherapy has not been explored clinically, evidence suggests that anti-HER2 agents may influence the immune microenvironment. Due to this potential, further investigation is needed to assess the impact of combination therapy on extending durable remissions in advanced disease and improving cure rates in the early-stage setting [102].

6.4 Monoclonal Antibodies

Trastuzumab is a humanized monoclonal antibody designed to target the HER2 receptor, which is overexpressed by some cancer cells, precisely 25 to 30% of breast cancers. It works by inhibiting the growth of tumor cells that overexpress HER2 by binding to the high-affinity domain of HER2. A well-designed multicenter study found that adding Trastuzumab to either an anthracycline plus cyclophosphamide or paclitaxel as first-line therapy for metastatic breast cancer significantly increased objective response rate, time to disease progression, duration of response, and overall survival compared to chemotherapy alone. When used as a single agent, Trastuzumab resulted in an objective response in 15% of extensively pretreated patients and 26% of previously untreated patients with metastatic breast cancer overexpressing HER2 [103].

Trastuzumab has demonstrated synergistic effects with various chemotherapy agents in preclinical studies, but the optimal clinical combination has yet to be identified. Most patients tolerate Trastuzumab well, although acute fever, chills, and potential cardiac issues are notable adverse reactions. Serious adverse events, such as

anaphylaxis and mortality, have been reported in 0.25% of patients. Additionally, symptomatic or asymptomatic cardiac dysfunction occurred in 27% of patients receiving anthracycline and cyclophosphamide in combination with Trastuzumab and 13% of those receiving Trastuzumab with paclitaxel. For patients receiving Trastuzumab alone, the occurrence was 4.7% [104].

Trastuzumab, when used alone or in combination with chemotherapy, has been shown to significantly improve the average time before disease progression and overall survival in patients with metastatic breast cancer that overexpresses HER2. However, there is a risk of heart problems, especially in patients with existing heart issues, older patients, and when used with or after anthracyclines. Trastuzumab can be used with paclitaxel as the first option for treatment or on its own for second or third-line treatment for patients with metastatic breast cancer overexpressing HER2. Ongoing research is focused on finding the best combination of Trastuzumab with other anticancer medications and the most effective timing, sequence, and duration of treatment in both pre-surgery and post-surgery settings [105].

Pertuzumab, a monoclonal antibody targeting the HER2 extracellular domain II region, is an innovative drug that effectively prevents HER2 heterodimerization and blocks the receptor-mediated signal transduction pathway. When used alongside trastuzumab, pertuzumab complements its action mechanism, resulting in a more potent blocking effect on HER2 downstream signaling. This combination has significantly enhanced treatment effectiveness in HER2-positive breast cancer patients while avoiding increased cardiotoxicity [106]. The US FDA has approved pertuzumab for various applications, including as a first-line treatment for HER2-positive advanced breast cancer, preoperative neoadjuvant therapy in early breast cancer patients, and treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapies or chemotherapy for metastatic diseases. Furthermore, pertuzumab was approved for

adjuvant treatment of HER2-positive early breast cancer in 2019. Overall, pertuzumab represents a significant advancement in the treatment of HER2-positive breast cancer across all stages [107].

Margetuximab, or MGAH22 or margetuximab-cmkb, is an advanced human/mouse chimeric and Fc-engineered monoclonal antibody explicitly targeting the HER2 receptor. This distinct antibody has a unique binding profile compared to trastuzumab, with increased affinity for CD16A (FcγRIIA) and reduced affinity for CD32B (FcγRIIB), leading to enhanced antibody-dependent cellular cytotoxicity (ADCC) and improved immune response activation. In December 2020, the US FDA approved the use of margetuximab in combination with chemotherapy for patients with metastatic HER2+ breast cancer who have previously undergone two or more HER2-targeted treatments based on the positive results from the SOPHIA trial. The approval marked a significant milestone, as margetuximab could moderately improve progression-free survival compared to trastuzumab in combination with chemotherapy. Ongoing studies are actively exploring the expanded role of margetuximab in various therapeutic settings, including early-stage breast cancer and gastrointestinal malignancies, representing a promising advancement in cancer treatment research [109].

6.5 Immune Checkpoint Inhibitors: Include Atezolizumab and Pembrolizumab

Atezolizumab Immunotherapy has emerged as a powerful tool in the fight against cancer by bolstering the body's immune response. Recent advances in immunotherapy, such as immune checkpoint inhibitors (ICIs), cytokines, adoptive T cell therapy (ACT), and cancer vaccines, have shown great potential in providing significant clinical benefits while causing minimal immune-related adverse events. Specifically, high immunogenicity breast cancers, including triple-negative and HER2-negative subtypes, have displayed remarkable responsiveness to ICI therapy. By targeting the PD-1/PD-L1 interaction, these therapies aim to activate cytotoxic T effector cells against breast cancer cells. Ongoing research

into the role of the PD-1/PD-L1 interaction within the breast cancer microenvironment is crucial. Recent findings have underscored the safety and effectiveness of combining anti-PD-1/L1 antibodies with systemic therapies like chemotherapy, targeted therapies, and radiotherapy. Atezolizumab, a carefully engineered PD-L1 inhibitor, has been designed to block the interaction of the PD-L1 ligand with its receptors, PD-1 and B7.1, thereby preventing antibody-dependent cellular cytotoxicity (ADCC) against T cells [111].

In March 2019, atezolizumab made history as the first immune checkpoint inhibitor to receive FDA approval specifically for the treatment of breast cancer, mainly when used in combination with nab-paclitaxel. The significant IMpassion 130 trial showed substantial improvements in progression-free survival and overall survival with interim analysis, resulting in the approval of the atezolizumab and nab-paclitaxel combination for the treatment of metastatic triple-negative breast cancer and unresectable locally advanced breast cancers. Atezolizumab, a new immunosuppressive inhibitor that targets the PD-L1 molecule within the tumor microenvironment, has shown significant clinical activity in metastatic TNBC. This marks a major milestone as the first FDA-approved ICI for advanced TNBC. Moreover, when combined with chemotherapy, atezolizumab has demonstrated enhanced antitumor immunity compared to its modest activity as a single agent [112].

Pembrolizumab is a PD-1 protein inhibitor. PD-1 protein is expressed on immune effector cells, such as T cells, B cells, natural killer cells, tumor-infiltrating lymphocytes (TILs), and dendritic cells. The interaction of PD-1 with PD-L1/L2 ligand leads to a decreased immune response. Pembrolizumab, a humanized monoclonal antibody, works by hindering this interaction, thereby preventing the blunting of the immune response against cancer cells. Studies have shown that pembrolizumab monotherapy has durable antitumor activity in advanced triple-negative breast cancer, with improved clinical responses observed among patients with higher programmed death ligand 1 (PD-L1)

expression. The phase 3 KEYNOTE-355 trial investigated whether adding pembrolizumab could enhance the anti-tumor effects of chemotherapy for patients with previously untreated locally recurrent, inoperable, or metastatic triple-negative breast cancer. However, some critical questions remain, such as identifying which patients would truly benefit from adding pembrolizumab, determining the optimal duration of therapy, and deciding on the best adjuvant therapy based on the pathologic response. Interim analysis data from a prespecified study showed that chemotherapy plus pembrolizumab significantly prolongs cancer-free survival compared to placebo plus chemotherapy among patients with a PD-L1 combined score of 10 or more. The combined positive score (CPS) is calculated by dividing the number of PD-L1--staining cells (tumor cells, lymphocytes, and macrophages) by the total number of viable tumor cells and multiplying the result by 100 [113].

VII. CONCLUSION: UNVEILING THE BLUEPRINT OF BREAST CANCER - A MOLECULAR REVOLUTION IN THERAPEUTICS

The landscape of breast cancer management has undergone a seismic shift with the advent of molecular and genetic profiling. These intricately woven tools, encompassing gene expression analysis, mutation detection, and copy number analysis, have shattered the one-size-fits-all archetype, revealing the intricate blueprint of individual tumors. This newfound knowledge of tumor biology fuels a personalized medicine revolution, empowering clinicians to tailor treatment strategies with unprecedented precision and optimize outcomes for each patient.

Multigene assays like Oncotype DX, MammaPrint, Prosigna, and Breast Cancer Index have risen as cornerstone tools, unlocking the doors to prognostication, treatment de-escalation, and targeted therapy selection. By dissecting the complex interplay of genes within a tumor, these assays guide decisions on chemotherapy necessity, predict response to endocrine therapy,

and identify actionable mutations for targeted therapies like PARP or CDK4/6 inhibitors. This stratified approach minimizes unnecessary toxicity, maximizes treatment efficacy, and improves patient quality of life. Beyond multigene assays, many tools like PIK3CA mutation testing, NTRK fusion detection, and PD-L1 expression analysis illuminate specific facets of the tumor's immunogenicity and potential for response to immunotherapy. This personalized approach to immunotherapy harnesses the power of the immune system to specifically target and eradicate tumors, offering a beacon of hope for patients who traditionally do not respond to conventional therapies.

However, the full potential of this revolution necessitates addressing existing challenges. Data interpretation and integration, standardization of testing protocols, and ensuring equitable access to these technologies remain crucial hurdles to overcome. Moreover, the dynamic nature of tumors necessitates the development of proactive approaches that can track tumor evolution and guide treatment adjustments in real time. In conclusion, molecular and genetic profiling marks a transformative chapter in breast cancer management. By unveiling the tumor's unique genetic blueprint, these powerful tools pave the way for personalized treatment strategies, optimized outcomes, and a future where each patient receives the most effective guideline-directed care possible. As research continues to refine these technologies and overcome existing challenges, we can envision a future where breast cancer is not a singular entity but a constellation of diverse tumor profiles; each met with a personalized therapeutic response. This is the promise of the molecular revolution in breast cancer: unveiling the blueprint, tailoring the therapy, and ultimately, conquering the disease.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Over the years, so much emphasis has been placed on raising girls to higher levels that society has forgotten about the boy child. At the time, society in Africa and particularly in Kenya was content with the boy child's position and unconsciously focused on the girl child to the alienation of the boy. The callous disregard for boys has caused a decline in their development and performance and caused an identity crisis. Consequently, a significant majority of the African boychild have grown into dysfunctional adults. The main objective of this research was to evaluate the role of social integration on the development of boy child in Kenya.

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ABSTRACT

Over the years, so much emphasis has been placed on raising girls to higher levels that society has forgotten about the boy child. At the time, society in Africa and particularly in Kenya was content with the boy child's position and unconsciously focused on the girl child to the alienation of the boy. The callous disregard for boys has caused a decline in their development and performance and caused an identity crisis. Consequently, a significant majority of the African boychild have grown into dysfunctional adults. The main objective of this research was to evaluate the role of social integration on the development of boy child in Kenya. The study used an explanatory research design. The target population unit of analysis was all the 3,500,000 students, 113,200 teachers, 10,463 principals, 3,400,000 parents, 14 heads of mental health hospitals, 129 heads of prisons, and 47 county education officers respectively in Kenya. Stratified-Systematic sampling and purposive sampling were used to identify a sample size of 1,682 respondents selected using the Krejcie and Morgan Table formula. The findings revealed a statistically significant positive moderate correlations between responsibilities ($r=0.11$, $p<0.05$), relationships ($r=0.12$, $p<0.05$), and mentorship ($r=0.33$, $p<0.01$) with boy child development suggest that these factors not only independently contribute to development but also interact synergistically to establish a robust framework for social integration. The findings from this study offer valuable insights for policymakers and implementers in addressing critical gender disparities and enhancing the development and performance of boys. This has broader implications for achieving the Sustainable Development Goals (SDGs), Africa Vision 2050, and Kenya Vision 2030.

Keywords: social integration, responsibilities, relationships and mentorship.

Author: Atlantic International University.

I. INTRODUCTION AND BACKGROUND TO THE STUDY

According to Business Daily Africa (2019) the boy child has been pushed into a wilderness of identity in the twenty-first century as a result of the convergence of modernization and conventional behaviours. Today's message is that a girl can achieve everything and even better than that a boy can. It is based on the belief that a girl child requires somebody to journey with her through the tumultuous stage of adolescence, as well as the misconception that a boy child is an impediment, if not an adversary, to a girl's development and achievement (Pike, 2020). In African culture, the boy child is generally assumed to know his way around, so he is expected to be stoic, strong, and forgiving. As such, he doesn't require guidance and, in fact, is the aggressor. It began in their households, wherein boys lacked a role model for how to mature into responsible adults. Broken society, generational loss, and dysfunctional families have resulted as a result of this (Pomerantz et al., 2013).

According to Lejaragga (2011) social integration is essential for a child's development, and children who have strong social networks tend to be more responsible, live longer, and live healthier lives. Furthermore, young adults and teens with disabilities who have positive social relationships with their peers and engage in engaging community and societal activities that they enjoy and value are more likely to be satisfied and successful as adults than those who are not involved (Berkel, 2018). There is a strong link between social integration and a child's

psychological well-being and mental health (Reynolds, 2021). Boys spend more time with peer groups during their development. A child develops a high level of social network centrality when he or she feels connected to friends, peers, parents, family, community, and school. Children who are less socially integrated have more internalizing problems, which leads to a higher risk of mental health disorders later in life. According to Rizvi (2021) research, social integration is positively associated with lower mortality among children from causes such as drug overdose and suicide, and it improves access to various forms of support and produces positive psychological states such as a sense of belonging and self-worth, which are important in preventing distress and boosting self-esteem. Poor mental health in childhood has been linked to lower social integration. Social integration has the potential to increase acceptance among children with and without disabilities, strengthen leadership skills, and promote overall development (Britto et al., 2021). Families, communities, schools, and society in general can help the boy child build and maintain social integration by believing that social integration is a good thing, identifying the activities that the child is passionate about, communicating to others the child's strengths, letting the child choose, developing an action plan, developing awareness of the skills that will support the child's social integration, and finding a bridgebuilder person who will help the child.

According to Chulani and Gordon (2014) from the beginning of adulthood, child development is a series of changes in physical features, thoughts, language, and emotional well-being. During this process, the child gains independence and lessens his reliance on his parents. According to Dahl (2004), this stage of a child's development is heavily influenced by psychosocial factors originating in their environment. As a result, child development can be actively aided by targeted therapeutic interventions and appropriate home-based practice. Healthy eating, physical activity, health, and the growth environment are all important considerations. Observing a child's development is critical to ensuring that the child

reaches all of their developmental milestones. It aids in the early detection of any problems in the child's development (LoBraico et al., 2020). Parents, teachers, and community health teams should strictly adhere to the developmental milestone checklist because it can guide them on what is abnormal as the child grows into adulthood and help them take corrective measures (Tucker et al., 2020). Even so, it is important to note that, while the development of a boy child follows a predictable pattern, each child is unique in their developmental journey, and the time frames in which they meet their developmental milestones may vary.

II. STATEMENT OF THE PROBLEM

According to a report released in 2016 by the Government of Kenya (GoK) through the Ministry of Education, there is an increased dropout rate and a growing proportion of boys marginalized in schools and tertiary training institutions (Ministry of Education, 2016). Seventy percent of the one million students who drop out of school each year are boys. According to the report, this is as a result of the boy child's development being neglected. Furthermore, the dropout rate among boys in the 23 sampled counties in 2016 was 3.3 percent, compared to 2.5 percent for girls. Boys were twice as likely as females to never be engaged in school and were 50 percent more likely to have been retained in grade at least once. According to data from situational analysis by UNICE (2017), boys are more likely than girls to have a difficult childhood, and boys have a higher suicide rate than girls. In 2018, the KNBS recorded 491 suicides, 330 of which were by boys (Star, 2020). Because of the gender disparity and the expectations placed on boys by society in Kenya, boys are more likely to suffer from depression than girls, and if not addressed, this will most likely follow the child throughout his or her life, resulting in a dysfunctional adult.

III. RESEARCH OBJECTIVE

To evaluate the role of social integration on the development of boy child in Kenya.

IV. LITERATURE REVIEW

According to Lejaragga (2011) social integration is essential for a child's development, and children who have strong social networks tend to be more responsible, live longer, and live healthier lives. Furthermore, young adults and teens with disabilities who have positive social relationships with their peers and engage in engaging community and societal activities that they enjoy and value are more likely to be satisfied and successful as adults than those who are not involved Berkel (2018). There is a strong link between social integration and a child's psychological well-being and mental health (Reynolds, 2021). Boys spend more time with peer groups during their development. A child develops a high level of social network centrality when he or she feels connected to friends, peers, parents, family, community, and school. Children who are less socially integrated have more internalizing problems, which leads to a higher risk of mental health disorders later in life. According to Rizvi (2021) research, social integration is positively associated with lower mortality among children from causes such as drug overdose and suicide, and it improves access to various forms of support and produces positive psychological states such as a sense of belonging and self-worth, which are important in preventing distress and boosting self-esteem. Poor mental health in childhood has been linked to lower social integration. Social integration has the potential to increase acceptance among children with and without disabilities, strengthen leadership skills, and promote overall development (Britto et al., 2021). Families, communities, schools, and society in general can help the boy child build and maintain social integration by believing that social integration is a good thing, identifying the activities that the child is passionate about, communicating to others the child's strengths, letting the child choose, developing an action plan, developing awareness of the skills that will support the child's social integration, and finding a bridgebuilder person who will help the child.

V. ECOLOGICAL SYSTEMS THEORY

Urie Bronfenbrenner, a Russian-born American developmental psychologist, pioneered the ecological systems theory, also known as development in context, in 1979. This theory provides a framework for arguing that everything in a child's developmental environment shapes their development. The child, according to Bronfenbrenner, is entangled in the various ecosystems of the family, school, and the most expansive ecosystem, which is comprised of community culture and society in general (Pilgrim, 2012). All of these systems interact, influence one another, and influence all aspects of a child's development, and as a child grows, their interaction with environmental factors becomes more complex. As a result, the complexity is expected to increase even further as the child's cognitive and physical structure matures into adulthood.

According to Bronfenbrenner's ecological systems theory, a child's interaction with their environment has a significant impact on the type of person they will become in adulthood Fraser (1996). As a child grows, their interactions with their environment become more delicate and complex. As children grow into adults, their cognitive, psychological, and sociological structures can become more complex. As a result, because nature follows a predetermined path, the environment that surrounds the child either hinders or enhances their development (Youngblade, 2007). According to Bronfenbrenner, the economy has created the most destructive force on a child's development by causing the unpredictability and instability of family life. The boy child no longer has the necessary constant interaction with important adults or mentors for his development. As a result, if the relationships within the immediate microsystems fail, the child will lack the tools needed to explore other systems. According to Kia-Keating et al. (2011) when a child does not receive the affirmations that he should receive from his family or other significant adults in his life, he will frequently seek this attention elsewhere. These flaws manifest as antisocial behavior, an inability to provide self-direction,

and a consistent lack of self-discipline. Bronfenbrenner recommends that the family, school, community, health institutions, and proper policy enactment and implementation address these psychosocial deficiencies in boy child development head on (Bonnaire et al., 2014). All of these institutions should work together to strengthen the primary relationship and to foster an environment that welcomes and nurtures children as they grow into responsible adults and fathers. To top it all off, it is in everyone's best interest to use this research to develop a relevant policy framework for boy child public policy that eases developmental conflicts and fosters social values that increase the value of work done on behalf of the boy child at all levels: parents, extended family, community, teachers, mentors, supervisors, and legislators.

5.1 Social Integration on the Development of boy Child

Hatch and Wandsworth (2012) examined the impact of adult social integration on child development in the British 1946 Birth Cohort and concluded that anxious or sad children struggled to integrate into adulthood throughout their lives. This was frequently associated with a decline in their overall life performance as well as mental illnesses. Furthermore, they frequently had strained relationships, unstable families, and were frequently divorced. Kamis and Copland (2020) conducted a study on the long arm of social

integration among children in peer connections and discovered that these children shape their mental health in gender-specific ways. The study discovered that low social integration predicted high depressive levels in both boys and girls from adolescence to adulthood. This study, on the other hand, was conducted in a developed country, which may not experience the same level of development as developing countries.

VI. METHODOLOGY

The study used an explanatory research design, with all 10,463 Kenyan public secondary schools serving as the unit of study. The target population unit of analysis was all the 3,500,000 students, 113,200 teachers, 10,463 principals, 3,400,000 parents, 14 heads of mental health hospitals, 129 heads of prisons, and 47 county education officers respectively in Kenya. Stratified-Systematic sampling and purposive sampling were used to identify a sample size of 1,682 respondents selected using the Krejcie and Morgan Table formula. This study employed a mixed-method research approach to collect and analyze both qualitative and quantitative data. For descriptive and inferential data analysis, SPSS version 24.0 was utilized data using mean, standard deviation, Pearson Product Moment Correlation and Multiple Regression. A pretest was done in Machakos county to ascertain validity and reliability of the research instruments.

VII. FINDINGS AND DISCUSSIONS

Table 1: Social Integration

| | N | Mean | Std. Dev |
|--|------|------|----------|
| The boy child actively participates in societal chores. | 1564 | 3.93 | 1.00 |
| The boy child efficiently cares for younger siblings and classmates. | 1564 | 4.00 | 0.81 |
| The boy child optimistically accepts responsibility for their decision-making choices. | 1564 | 3.71 | 1.13 |
| The boy child frequently expresses his views and feelings to close classmates. | 1564 | 3.93 | 1.00 |
| Through collaborative approaches, the child develops friendships, teamwork, and problem-solving abilities. | 1564 | 4.04 | 0.98 |
| With ease, the boy child initiates contact and resolves disputes constructively. | 1564 | 4.14 | 1.02 |

| | | | |
|---|------|------|------|
| The boy child is eager to pick up new skills, knowledge, and competence. | 1564 | 3.57 | 1.13 |
| The boy child has a positive attitude towards future learning and progress. | 1564 | 3.93 | 1.00 |
| In life, the child arouses enthusiasm for mentoring others | 1564 | 3.72 | 1.23 |

Source: Nzioka (2023)

The boy child actively participates in societal chores (Mean = 3.93, Std. Dev = 1.00): The high mean of 3.93 suggests a strong agreement that the boy child actively engages in societal chores. The low standard deviation of 1.00 indicates a relatively low level of variability in responses, implying a general consensus among respondents. The boy child efficiently cares for younger siblings and classmates (Mean = 4.00, Std. Dev = 0.81): The maximum mean of 4.00 indicates a high level of agreement that the boy child efficiently cares for younger siblings and classmates. The low standard deviation of 0.81 suggests a high level of consensus among respondents with minimal variation in opinions.

The boy child optimistically accepts responsibility for their decision-making choices (Mean = 3.71, Std. Dev = 1.13): The mean of 3.71 suggests a moderate level of agreement regarding the boy child's optimistic acceptance of responsibility for decision-making. The standard deviation of 1.13 indicates variability in responses, suggesting differing opinions among respondents. The boy child frequently expresses his views and feelings to close classmates (Mean = 3.93, Std. Dev = 1.00): The high mean of 3.93 suggests strong agreement that the boy child frequently expresses views and feelings to close classmates. The low standard deviation of 1.00 indicates a relatively low level of variability, reflecting a consistent perception among respondents. Through collaborative approaches, the child develops friendships, teamwork, and problem-solving abilities (Mean = 4.04, Std. Dev = 0.98): The mean of 4.04 indicates a high level of agreement that collaborative approaches foster the development of friendships, teamwork, and problem-solving abilities. The standard deviation of 0.98 suggests a relatively low level of variability, indicating a consensus among respondents.

With ease, the boy child initiates contact and resolves disputes constructively (Mean = 4.14, Std. Dev = 1.02): The high mean of 4.14 indicates a strong agreement that the boy child initiates contact and resolves disputes constructively. The standard deviation of 1.02 suggests a moderate level of variability, implying some diversity in opinions among respondents. The boy child is eager to pick up new skills, knowledge, and competence (Mean = 3.57, Std. Dev = 1.13): The mean of 3.57 suggests a moderate level of agreement regarding the boy child's eagerness to acquire new skills, knowledge, and competence. The standard deviation of 1.13 indicates variability in responses, suggesting diverse opinions among respondents. The boy child has a positive attitude towards future learning and progress (Mean = 3.93, Std. Dev = 1.00): The high mean of 3.93 suggests strong agreement that the boy child maintains a positive attitude towards future learning and progress. The low standard deviation of 1.00 indicates a relatively low level of variability, reflecting a consistent perception among respondents.

In life, the child arouses enthusiasm for mentoring others (Mean = 3.72, Std. Dev = 1.23): The mean of 3.72 suggests a moderate level of agreement that the boy child arouses enthusiasm for mentoring others. The higher standard deviation of 1.23 indicates greater variability in responses, suggesting differing opinions among respondents. The descriptive statistics provide a comprehensive overview of respondents' perceptions of a boy child's social integration. High means generally indicate positive agreement, while standard deviations highlight the level of consensus or diversity in opinions among respondents.

Table 2: Correlations Related to the Constructs of Social Integration and Development of Boy Child

| | | Development of boy child | Responsibilities | Relationships | Mentorship |
|--------------------------|---------------------|--------------------------|------------------|---------------|------------|
| Development of boy child | Pearson Correlation | 1 | | | |
| | Sig.(2-tailed) | | | | |
| Responsibilities | Pearson Correlation | 0.11* | 1 | | |
| | Sig.(2-tailed) | 0.00 | | | |
| Relationships | Pearson Correlation | 0.12* | 0.32** | 1 | |
| | Sig.(2-tailed) | 0.00 | 0.00 | | |
| Mentorship | Pearson Correlation | 0.33** | 0.19* | 0.22* | 1 |
| | Sig.(2-tailed) | 0.00 | 0.00 | 0.00 | |

Source: Nzioka (2023)

Table 39 presents correlations related to the constructs of social integration and the development of boy child in Kenya, highlighting the interconnectedness between various psychosocial factors and their impact on developmental outcomes within this population. Firstly, there is a significant positive correlation between the development of boy child and their engagement in responsibilities ($r = 0.11$, $p < 0.05$). While the correlation coefficient is relatively small, the significance suggests that involvement in responsibilities may contribute, albeit modestly, to the overall developmental trajectory of boy child in Kenya. Furthermore, significant positive correlations are observed between the development of boy child and both their relationships with others ($r = 0.12$, $p < 0.05$) and their engagement in mentorship activities ($r = 0.33$, $p < 0.01$). These findings indicate that positive social relationships and mentorship experiences may play more substantial roles in influencing the developmental outcomes of boy child in Kenya. Additionally, a significant positive correlation is found between responsibilities and relationships ($r = 0.32$, $p < 0.01$), suggesting that involvement in responsibilities may be associated with the quality and dynamics of social relationships among boy child. This underscores the interconnectedness between social roles and interpersonal interactions in shaping developmental outcomes within this population. Moreover, there are significant positive correlations between responsibilities and

mentorship ($r = 0.19$, $p < 0.05$) and between relationships and mentorship ($r = 0.22$, $p < 0.05$), indicating potential synergistic effects between these psychosocial factors in promoting positive developmental outcomes among boy child in Kenya.

Overall, these findings highlight the importance of social integration and engagement in responsibilities, relationships, and mentorship activities in shaping the developmental trajectories of boy child in Kenya. By fostering supportive social environments and providing opportunities for meaningful engagement in various roles and activities, interventions can promote the holistic development and well-being of boy child within their communities.

Table 3: Coefficients ‘Measures of Social Integration effect on the Development of boy Child’

| Coefficients | | | | | |
|-------------------------------------|-----------------------------|--------------|---------------------------|--------------|--------------|
| Model | Unstandardized coefficients | | Standardized coefficients | T | Sig. |
| | B | Std. Error | Beta | | |
| (Constant) product Responsibilities | 1.83 0.49 | 0.24 0.21 | 0.29 | 7.38 2.32 | 0.00 0.00 |
| Relationships | 0.65 | 0.23 | 0.23 | 2.78 | 0.00 |
| Mentorship | 0.64 | 0.28 | 0.63 | 2.28 | 0.00 |

Source: Nzioka (2023)

Table 53 offers a comprehensive examination of coefficients derived from a regression model, providing a nuanced understanding of how different facets of social integration impact the development of boy child within the realm of public health. Each coefficient serves as a crucial piece of evidence illuminating the intricate relationship between social dynamics and positive developmental outcomes for boys. Firstly, the constant term associated with product responsibilities sets a baseline for boy child development in the absence of explicit social integration factors. With a value of 1.83, it suggests that even without specific interventions promoting responsibilities, there exists a foundational level of development among boy child. Delving deeper into the coefficients, the analysis highlights the significant contributions of responsibilities, relationships, and mentorship to boy child development. For product responsibilities, the coefficient of 0.24 indicates that for every unit increase in responsibilities undertaken by boys, there is a corresponding increase of 0.24 units in their overall development. This underscores the importance of engaging boys in meaningful tasks and duties within their social environment, fostering a sense of purpose and accomplishment. Moving to relationships, the coefficient of 0.65 underscores the pivotal role of quality relationships in nurturing positive developmental outcomes for boys. This suggests that for every unit increase in the quality or quantity of relationships, there is a corresponding increase of 0.65 units in boy child development. It emphasizes the significance of fostering supportive and nurturing relationships

within the social fabric surrounding boys, providing them with a sense of belonging and emotional support critical for their well-being.

Similarly, the coefficient for mentorship, standing at 0.64, highlights the profound impact of mentorship on boy child development. This suggests that for every unit increase in mentorship received by boys, there is a corresponding increase of 0.64 units in their overall development. Mentorship offers guidance, support, and role modeling, enabling boys to navigate challenges, acquire valuable skills, and build resilience in the face of adversity. The statistical significance of these coefficients, with all associated significance levels (Sig.) being 0.00, reinforces the robustness of the observed relationships. It indicates that the impact of responsibilities, relationships, and mentorship on boy child development is not merely coincidental but rather statistically meaningful, lending credence to the importance of these social integration factors in shaping the developmental trajectories of boys.

Drawing from the findings in Table 53, the following statistical model can be used to predict the Development of boy child’ based on a one standard deviation increase in social integration measures:

$$\text{Development of boy child} = 1.83 + 0.29\text{Res.} + 0.23\text{Rel.} + 0.63\text{Men.} + \epsilon.$$

Where:

1.83 is the y-intercept; constant

0.29, 0.23, 0.63 = an estimate of the expected increase in the Development of boy child’

corresponding to an increase in social integration.

RR is the Responsibilities

Rel. is the Relationships

Ment. is the Mentorship

ε = Error term

The coefficients derived from this analysis provide compelling evidence of the multifaceted influence of social integration on the development of boy child in the public health domain. By highlighting the significance of responsibilities, relationships, and mentorship, these findings underscore the importance of cultivating supportive social environments to nurture positive developmental outcomes for boys. They offer valuable insights for designing targeted interventions and policies aimed at enhancing the overall well-being and resilience of boy child within the broader public health framework.

VIII. CONCLUSIONS

The developmental trajectory of a boy child is significantly shaped by various elements of social integration, as evidenced by the data presented in this study. These findings agree with those of Hatch and Wandsworth (2012) examined the impact of adult social integration on child development in the British 1946 Birth Cohort and concluded that anxious or sad children struggled to integrate into adulthood throughout their lives. This was frequently associated with a decline in their overall life performance as well as mental illnesses. Furthermore, they frequently had strained relationships, unstable families, and were frequently divorced. Kamis and Copland (2020) conducted a study on the long arm of social integration among children in peer connections and discovered that these children shape their mental health in gender-specific ways. The study discovered that low social integration predicted high depressive levels in both boys and girls from adolescence to adulthood.

In the current study social integration, encompassing responsibilities, relationships, and mentorship, plays a crucial role in fostering not

only the boy child's personal growth but also his ability to contribute meaningfully to society. By analyzing the correlation and regression data, this conclusion will focus on how these three primary elements impact the boy child's development, while also linking the statistical findings to the broader social framework. The data strongly indicates that the responsibilities undertaken by a boy child are a foundational element in shaping his development. Table 36 highlights a significant positive correlation between the boy child's active participation in societal chores and caregiving roles, suggesting that taking on responsibilities directly influences a child's competence in household and peer-related tasks. Specifically, the Pearson correlation of 0.67 ($p < 0.01$) indicates that when boys engage in chores, they are more likely to exhibit greater efficiency in caring for siblings and classmates, promoting a sense of responsibility and duty. The strong correlation between a boy child frequently expressing views and feelings to classmates and collaborative approaches ($r = 0.67$, $p < 0.01$) highlights the significance of open communication and teamwork in promoting relational skills. Relationships foster communication, emotional intelligence, and the ability to work within a team, which are essential for social development. Additionally, the correlation between the boy child's ability to initiate contact and resolve disputes constructively and his communication and teamwork skills ($r = 0.32$, $p < 0.01$; $r = 0.33$, $p < 0.01$) shows that social problem-solving is closely linked to relational success. These findings support the idea that boys who develop effective communication and conflict resolution skills are better equipped to build positive and supportive relationships with their peers, which in turn contributes to their overall social well-being and emotional development.

VIII. RECOMMENDATIONS

8.1 Practice Recommendations

To effectively harness the elements of social integration for the development of the boy child, practitioners should focus on implementing structured programs that foster responsibility, relationships, and mentorship within various

environments—schools, homes, and community organizations. **Responsibility Programs:** Develop initiatives that encourage boys to take on household chores, community service projects, and peer mentoring roles. These programs should be designed to ensure that boys experience tangible outcomes from their responsibilities, such as recognition or opportunities to lead, which will reinforce the importance of their contributions. **Communication and Relationship Building Workshops:** Facilitate workshops that teach boys effective communication and conflict resolution skills. These could involve role-playing scenarios where boys practice expressing their feelings, negotiating, and resolving disputes amicably. Such workshops should be inclusive, allowing boys to engage in collaborative activities that foster teamwork and emotional intelligence. **Mentorship Initiatives:** Establish mentorship programs that connect boys with positive role models in their communities. This could include pairing them with older students, community leaders, or professionals who can guide them in developing personal, academic, and vocational skills. These programs should include structured activities that promote skill acquisition and the sharing of experiences, thereby enhancing both the mentor's and mentee's development. **Parent and Community Engagement:** Encourage parents and community members to actively participate in the developmental processes of boys. Organizing community events where parents can engage with their children in responsibility-oriented tasks can foster a sense of community and shared purpose, reinforcing the importance of social integration in development.

8.2 Policy Recommendations

Policymakers should focus on creating and supporting frameworks that facilitate the social integration of boys through formal and informal channels. **Funding for Educational and Community Programs:** Allocate resources to support educational institutions and community organizations in developing programs focused on responsibility, relationships, and mentorship. This funding should be aimed at initiatives that specifically target the social and emotional development of boys. **Curriculum Integration:**

Mandate the integration of social skills training into school curricula. Schools should be required to include modules on communication, teamwork, and conflict resolution, ensuring that boys learn these skills in a structured environment alongside their academic studies. **Support for Mentorship Networks:** Develop policies that encourage the establishment of mentorship networks within communities. This can include incentives for organizations that facilitate mentorship opportunities for boys, ensuring these networks are accessible and inclusive. **Research and Evaluation:** Establish guidelines for evaluating the effectiveness of programs aimed at fostering social integration. Policymakers should support research initiatives that explore the impact of responsibility, relationships, and mentorship on boy child development, allowing for evidence-based adjustments to existing programs.

8.3 Research Recommendations

Future research should delve deeper into understanding the complexities of social integration and its impact on the development of the boy child. **Longitudinal Studies:** Conduct longitudinal studies to track the long-term effects of social integration factors on the developmental trajectories of boys. Such studies could provide insight into how early experiences of responsibility, relationship-building, and mentorship influence adult outcomes. **Diverse Populations:** Expand research to include a diverse range of populations, examining how cultural, socioeconomic, and environmental factors influence the dynamics of social integration and its effects on boys. This would allow for more inclusive and comprehensive understandings of best practices. **Intervention Effectiveness:** Investigate the effectiveness of various interventions aimed at enhancing social integration among boys. Research should compare different approaches to responsibility-taking, relationship-building, and mentorship, providing insights into which strategies yield the best developmental outcomes. **Qualitative Research:** Incorporate qualitative methods to gather rich, detailed insights from boys about their experiences with social integration. This could include interviews and focus groups,

allowing researchers to understand the nuances of how boys perceive their responsibilities, relationships, and mentorship experiences. By addressing these areas through practice, policy, and research, stakeholders can significantly enhance the developmental outcomes for boys, ensuring they are equipped with the skills and competencies necessary for positive.

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Effectiveness of Wobenzym in Combined Therapy of Chronic Bacterial Prostatitis. Results of Systematic Review and Meta-Analysis

*Yuriy A. Kupriyanov, Andrey V. Zaitsev, Alexander N. Bernikov, Lyubov A. Khodyreva
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ABSTRACT

A systematic review and meta-analysis of research data on the effectiveness of the drug Wobenzym in the treatment of chronic bacterial prostatitis was performed. The aim of this study was to evaluate the efficacy of Wobenzym in the complex therapy of chronic bacterial prostatitis. The analysis included randomized and non-randomized controlled studies of the effectiveness of Wobenzim in the complex therapy of chronic bacterial prostatitis. The search was conducted in the databases CENTRAL, PubMed, ICTRP, eLibrary, ClinicalTrials.gov., Google Scholar, CyberLeninka, and search engines. The meta-analysis was conducted using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Statistical heterogeneity was assessed using the Cochran test and visually when constructing forest plots. A random effects model and a fixed effect model were used. Works published over the entire period were analyzed, 712 publications were identified. Nine publications fully met the stated criteria; all studies were non-randomized controlled studies. The final analysis included the results of 1292 patients.

Keywords: chronic bacterial prostatitis; Wobenzym; meta-analysis.

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Effectiveness of Wobenzym in Combined Therapy of Chronic Bacterial Prostatitis. Results of Systematic Review and Meta-Analysis

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ABSTRACT

A systematic review and meta-analysis of research data on the effectiveness of the drug Wobenzym in the treatment of chronic bacterial prostatitis was performed. The aim of this study was to evaluate the efficacy of Wobenzym in the complex therapy of chronic bacterial prostatitis. The analysis included randomized and non-randomized controlled studies of the effectiveness of Wobenzim in the complex therapy of chronic bacterial prostatitis. The search was conducted in the databases CENTRAL, PubMed, ICTRP, eLibrary, ClinicalTrials.gov., Google Scholar, CyberLeninka, and search engines. The meta-analysis was conducted using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Statistical heterogeneity was assessed using the Cochran test and visually when constructing forest plots. A random effects model and a fixed effect model were used. Works published over the entire period were analyzed, 712 publications were identified. Nine publications fully met the stated criteria; all studies were non-randomized controlled studies. The final analysis included the results of 1292 patients. Meta-analysis demonstrated the superiority of complex therapy including Wobenzym compared to treatment without Wobenzym in all studied parameters: eradication of the pathogen, decreased quality of life (QoL) scores, an increase in the linear speed of blood flow in the veins and peak systolic blood flow velocity in the arteries of the prostate gland, maximum urine flow rate, reduction in the number of points of the NIH-CPSI "Pain" subscale (difference 5 points) and NIH-CPSI "Quality of Life" subscale. The use of therapy including Wobenzym in patient s with chronic

prostatitis leads to a greater increase in the number of CDA⁺, CD8⁺ lymphocytes, phagocytic activity of lymphocytes, the level of complement CH-100 and immunoglobulins M, G, A. A systematic review/meta-analysis revealed an evident, significant, positive effect of the drug Wobenzym in the complex therapy of patients with chronic bacterial prostatitis, which is associated with its pathogenetic orientation in relation to this group of patients.

Keywords: chronic bacterial prostatitis, wobenzym, meta-analysis.

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I. INTRODUCTION

Chronic prostatitis is common in young and middle-aged men [1, 2]. The incidence of chronic prostatitis ranges from 2.2% to 9.7% worldwide [2, 3]. There has been a progressive increase in

the disease incidence over the past years [4-6]. The origin and progression of chronic inflammatory process in the prostate gland is based on a complex of pathological reactions: anatomic and physiological peculiarities of the organ, the presence of a pathogenic microorganism, which has the ability to adhere and form biofilm; microcirculatory disorders, fibrosis formation [7, 8].

The main complaints of patients during exacerbation of chronic bacterial prostatitis (CBP) are pain, sexual dysfunction, urinary disorders, and psychoemotional disorders [9, 10]. Modern approaches to the treatment of CBP are based on complex therapy. First of all, the use of antibacterial drugs is indicated. The European Association of Urologists in 2023 recommended using fluoroquinolones despite the high level of uropathogen resistance to them.

Fluoroquinolones are recommended as first-line drugs in the empirical treatment of CBP because of their favourable pharmacokinetic properties, good safety profile as a whole and antibacterial activity against Gram-negative microorganisms [11]. A combination of antibacterial drugs with various herbal extracts and alternative medicines with pathogenetic orientation is recommended [12, 13]. However, many patients still have complaints even after the end of treatment [14], which is often associated with the lack of eradication of the causative agent of CBP [9], disorders of the immune response and the course of the local inflammatory process with formation of connective tissue fibrous elements in the prostate tissue.

Thus, the high prevalence of CBP, recurrent or prolonged course of the inflammatory process, growth of uropathogen resistance are the basis for the search of drugs that could improve the outcome of treatment and provide the possibility of their long-term use in the combined therapy and subsequent prevention of recurrences of the disease.

To achieve success in the treatment of patients with CBP, drugs that either target individual components or comprehensively affect many links

of pathogenesis are used as adjuvant/alternative therapy. Such drugs include Wobenzym, a combination of highly active enzymes of plant and animal origin. It includes pancreatin, papain, bromelain, trypsin, lipase, amylase, chymotrypsin, and rutoside trihydrate.

Wobenzym, as described in instructions for medical use, has anti-inflammatory, immunomodulatory, fibrinolytic, antiplatelet, anti-edema and secondary analgesic action¹. Combinations of enzymes potentiate the action of antibacterial drugs [15]. This is achieved due to the ability of Wobenzym to improve the delivery of etiotropic drugs to the site of infection, increase the availability of the receptor apparatus of the host cell and pathogen, reduce the acidity of the environment in the site of inflammation, change the properties of microbial biofilms [16]. Enzymes increase the phagocytic and cytotoxic activity of immunocytes (monocytes/macrophages, natural killer cells, T-lymphocytes). The therapeutic effect of Wobenzym is realized through the influence on the inflammatory process, immunity, vascular and platelet haemostasi² [17]. Determination of the efficacy of the drug in the therapy of CBP is a relevant issue that requires additional research.

II. RELEVANCE OF SYSTEMATIC REVIEW

To date, no meta-analysis findings on the efficacy of Wobenzym in CBP have been published. Therefore, important questions remain: how does it affect the frequency of pathogen eradication? What is the impact on symptoms and quality of life for patients with CBP? How do the blood flow status and urine flow rate change with its inclusion in the complex therapy of CBP?

The study aims to evaluate the efficacy of Wobenzym in the complex therapy of CBP.

We included in the review the randomized and non-randomized controlled trials on the efficacy of the drug in the complex therapy of CBP. The

¹ Instructions for medical use of the medicinal product Wobenzym JIII-#(002667)-(PT-RU) dated 30/06/2023. <https://grls.minzdrav.gov.ru/lnstrlmg/2023/07/13/1495064/c9c87bad-c031-41fb-b6eb-1fe76b5d97fd.pdf>

² In the same place.

study included patients with CBP, regardless of age, race, or social status. We compared comprehensive therapy of CBP including Wobenzym and therapy not including Wobenzym. Endpoints have been identified.

Primary endpoint:

Frequency of pathogen eradication after therapy.

Secondary endpoints:

1. Change in Quality of Life (QoL) scores after treatment.
2. Change in prostate ultrasound data (peak systolic blood flow velocity in arteries, linear blood flow velocity in veins) after treatment. Change in maximum urine flow rate after treatment.
3. Change in National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) scores after therapy (Pain and Quality of Life subscales),
4. Changes in immunogram parameters after therapy.

2.1 Searching in Electronic Databases

Searching was carried out in the following databases: PubMed(<https://www.nlm.nih.gov>), using search words: "clinical trial," "humans," "Wobenzym," "prostatitis"; Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library, <https://www.cochranelibrary.com/central>), National Institutes of Health Ongoing Trials Register Clinical Trials.gov (www.clinicaltrials.gov), World Health Organization International Clinical Trials Registry Platform (ICTRP, <https://www.who.int/ictrp/en/>), using search words: 'Wobenzym'; Google Scholar (<https://scholar.google.ru/>), using search words: "clinical trial", "Wobenzym", "prostatitis", "study"; eLibrary.ru(<http://elibrary.ru>), using search words: "Wobenzym", "prostatitis"; Cyber Leninka (<http://cyberleninka.ru>), using search words: "clinical trial", "Wobenzym", "prostatitis", "study"; "Gray Zone" (search engine data), using search words: "clinical trial", "Wobenzym", "prostatitis", "study".

2.2 Assessment of Study Heterogeneity

The degree of heterogeneity was assessed visually by plotting "forest plots". In addition, the

quantitative evaluation with calculation of chi-square criterion (p threshold <0.10), I^2 , τ^2 was carried out. The following interpretation of the heterogeneity for values of I^2 was used: 0-25%, no heterogeneity; 25-50%, low; 50-75%, moderate; more than 75%, high.

2.3 Bias Assessment

The risk of bias was assessed using the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins J., 2021) [18] for randomized and non-randomized trials. The assessment was based on the recommendations of the Cochrane Community [19] using a validated questionnaire by O.Y. Rebrova et al. (2015) [20]. Data visualization was performed using the robvis application [21]. We categorized the risk of bias as "low," "high," or "unclear" for each study individually and for all studies. Any disagreements that arose at any stage were resolved through discussion.

2.4 Data Synthesis

For data synthesis, we used the conservative assumption that in all papers the authors provided data in SE format, with subsequent conversion for calculations into standard deviation (SD) using the formula $SD = SE \times \sqrt{n}$, where n is the number of patients in the group. The analysis was performed using the R programming language and the RStudio development environment (R version).

2.5 Generalization and Interpretation of Results

We used the GRADE approach to interpret the results [22].

2.6 Search Results

By searching and selecting studies that met the inclusion criteria, 9 out of 712 articles were selected for analysis (Figure 1).

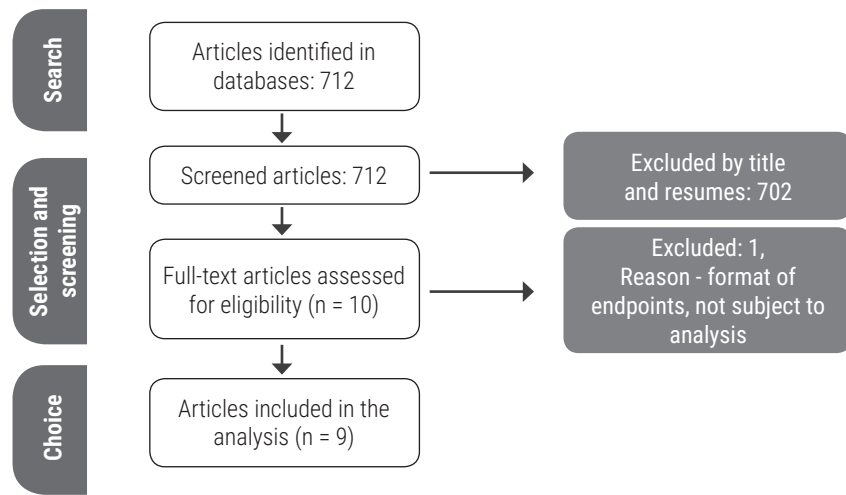


Fig. 1: Block diagram PRISMA [23]

| | | Risk of bias domains | | | | | | | |
|-------|-----------------|----------------------|----|----|----|----|----|----|--|
| | | D1 | D2 | D3 | D4 | D5 | D6 | D7 | |
| Study | Dosta, 2013 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | <div>Domains:</div> <div>D1: Bias due to confounding.</div> <div>D2: Bias due to selection of participants.</div> <div>D3: Bias in classification of interventions.</div> <div>D4: Bias due to deviations from intended interventions.</div> <div>D5: Bias due to missing data.</div> <div>D6: Bias in measurement of outcomes.</div> <div>D7: Bias in selection of the reported result.</div> <div>Judgement</div> <div>⊖ Moderate</div> <div>⊕ Low</div> <div>⊙ No information</div> |
| | Ershov, 2007 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Kodiri, 2013 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Noskov, 2004 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Tkachuk, 2015 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Tkachuk, 2007 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Solihov, 2009 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Dzhalilov, 2020 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |
| | Dzhalilov, 2019 | ⊖ | ⊖ | ⊕ | ? | ? | ? | ? | |

Figure 2: Estimation of bias by study. D1 - bias due to confounding; D2 - bias due to selection of participants; D3 - bias in classification of interventions; D4 - bias due to deviations from intended interventions; D5 - bias due to missing data; D6 - bias in measurement of outcomes; D7 – bias in selection of the reported outcome; Low; Moderate; No information available.

We did not rate any of the studies as being at high risk of bias in all areas (Figure 2). The characterization of the studies is given in Table 1.

III. RESULTS

The review included 9 non-randomized studies enrolling 1292 patients with CBP. The studies were published in Russian in the period from 2004 to 2020.

Table 1: Main Characteristics of Included Studies

Frequency of pathogen eradication after therapy

The above parameter has been provided appropriately in the following articles: Dosta N.I.(2013) [15], Ershov E.V. (2007) [25], Noskov N.Yu. (2004) [27], Tkachuk V.N. (2015) [28], Tkachuk V.N. (2007) [29] (Table 2).

| Author, year | Disease | Randomization | Participants, n | Average age | Experimental group | | Control group | |
|-----------------------------|---------|---------------|-----------------|-------------|--------------------|--|---------------|---|
| | | | | | n | therapy | n | therapy |
| Dzhalilov H.N. (2020) [24] | CBP | no | 84 | 67.5 | 44 | Drugs that improve microcirculation and hemodynamics in the prostate gland, antibiotics, Polioxidonium, Wobenzym | 40 | Drugs that improve microcirculation and hemodynamics in the prostate gland, antibiotics |
| Dosta N. I. (2013) [15] | CBP | no | 35 | 21.0 ± 7.9 | 20 | Antibiotics, Wobenzym | 15 | Antibiotics |
| Ershov E. V. (2007) [25] | CBP | no | 239 | 25.6 ± 3.5 | 66 | Antibiotics, Wobenzym | 40 | Antibiotics |
| Kodiri T. R. (2013) [26] | CBP | no | 68 | - | 28 | Antibiotics, Wobenzym | 40 | Antibiotics |
| Noskov N.Yu. (2004) [27] | CBP | no | 110 | - | 70 | Antibiotics, Wobenzym | 40 | Antibiotics |
| Tkachuk V. N. (2015) [28] | CBP | no | 250 | 28.6 ± 4.5 | 210 | Antibiotics, Wobenzym | 40 | Antibiotics |
| Tkachuk V.N. (2007) [29] | CBP | no | 237 | 28.3 ± 2.9 | 70 | Antibiotics, Wobenzym | 65 | Antibiotics |
| Solihov D.N. (2009) [30] | CBP | no | 135 | 33.5 ± 4.6 | 70 | Antibiotics, Wobenzym | 65 | Antibiotics |
| Dzhalilov H. N. (2019) [31] | CBP | no | 134 | - | 67 | Antibiotics, Wobenzym | 67 | Antibiotics |

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Table 2: Results of Studies on Eradication of Uropathogens

| Author, year | Experimental group | | | Control group | | |
|---------------------------|--------------------|----------------------------|-----------------|---------------|----------------------------|-----------------|
| | n | uropathogen growth rate, % | | n | uropathogen growth rate, % | |
| | | before treatment | after treatment | | before treatment | after treatment |
| Dosta N. I. (2013) [15] | 20 | 100 | 47 | 15 | 100 | 73.0 |
| Ershov E. V. (2007) [25] | 66 | 100 | 4.5 | 40 | 100 | 37.5 |
| Noskov N. Yu. (2004) [27] | 70 | 100 | 4.3 | 40 | 100 | 35 |
| Tkachuk V. N. (2015) [28] | 210 | 100 | 3.8 | 40 | 100 | 44.5 |
| Tkachuk V. N. (2007) [29] | 70 | 100 | 4.3 | 65 | 100 | 35.3 |

Table 3: Eradication Rates and Eradication Odds Ratios of Uropathogens for Each Study

| Study | Experimental group | | Control group | | OR | 95% CI | |
|---------------------------|--------------------|--------|---------------|--------|-------|-------------|-------------|
| | n | events | n | events | | lower limit | upper limit |
| Dosta N. I. (2013) [15] | 20 | 11 | 15 | 4 | 3.36 | 0.79 | 14.25 |
| Ershov E. V. (2007) [25] | 66 | 63 | 40 | 25 | 12.60 | 3.35 | 47.32 |
| Noskov N. Yu. (2004) [27] | 70 | 67 | 40 | 26 | 12.03 | 3.19 | 45.32 |
| Tkachuk V. N. (2015) [28] | 210 | 202 | 40 | 23 | 18.66 | 7.26 | 48.00 |
| Tkachuk V. N. (2007) [29] | 70 | 67 | 65 | 42 | 12.23 | 3.46 | 43.27 |

Note. Or, Odds Ratio; Ci, Confidence Interval

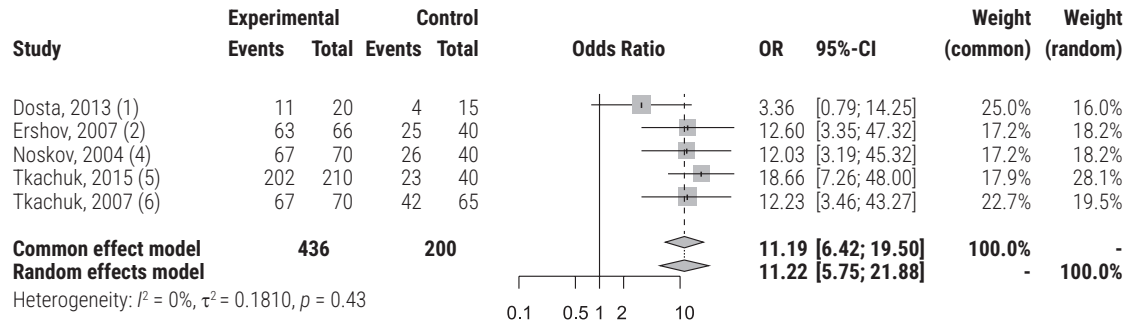


Figure 3: Meta-Analysis of the Rate of Eradication of Pathogens after Therapy with Wobenzym

The results show no heterogeneity ($I^2 = 0\%$), $\tau^2 = 0.18$ and 0.005 , $p > 0.10$. Moreover, 95% confidence interval (CI) of the pooled odds ratio (OR) calculated for both the fixed effects model and the random effects model did not overlap the number 1 (Table 3, Figure 3).

Thus, the use of therapy including Wobenzym in patients with CBP, significantly more often leads to eradication of the pathogen compared to therapy without Wobenzym. The OR of the fixed effects model is 11.19 (95% CI 6.42-19.50; $p = 0$), the OR of the random effects model is 11.22 (95% CI 5.75-21.88; $p = 0$).

3.1 Change in QOL Scores after Treatment with Wobenzym

The above parameter has been provided appropriately in the following articles: Dosta N.I. (2013) [15], Dzhililov H.N. (2020) [24], Dzhililov H.N. (2019) [31] (Table 4).

The results show low heterogeneity in the data ($I^2 = 32\%$), $\tau^2 = 0.17$, $p > 0.10$. At the same time, the 95% CI of the pooled difference of the mean values of QoL score reduction, calculated for both fixed and random effects models, does not overlap the zero value, which indicates a positive effect of treatment on the quality of life of patients (Fig. 4).

Thus, the use of therapy, including Wobenzym in patients with CBP, significantly reduces the QoL scores compared to therapy without Wobenzym, which means an improvement in the quality of life of these patients. Difference in mean values (MD) in the fixed effects model is -2.02 (95% CI -2.44... -1.59; $p = 0$); in the random effects model, it is -1.82 (95 % CI -2.54...-1.11; $p = 0$).

3.2 Changes in Linear Blood Flow Velocity in Prostatic Veins after Treatment

The above parameter has been provided appropriately in the following articles: Ershov

E.V. (2007) [25], Tkachuk V.N. (2015) [28] (Table 5).

The results show low heterogeneity in the data ($I^2 = 42\%$), $\tau^2 = 0.17$, $p > 0.10$. In this case, the 95%

CI of the pooled mean difference calculated for both the fixed and random effects model does not overlap the zero value (Figure 5)

Table 4: Quality of Life Parameters on the QOL Score According to Study Data

| Study | Experimental group | | | Control group | | | MD | 95% CI | |
|----------------------------|--------------------|-----|------|---------------|-----|------|------|-------------|-------------|
| | n | M | SD | n | M | SD | | lower limit | upper limit |
| Dzhalilov H.N. (2019) [31] | 44 | 1.8 | 1.33 | 40 | 4.0 | 0.89 | -2.2 | -2.68 | -1.72 |
| Dzhalilov H.N. (2020) [24] | 51 | 2.7 | 2.14 | 51 | 4.2 | 3.57 | -1.5 | -2.64 | -0.36 |
| Dosta N.I. (2013) [15] | 20 | 1.0 | 3.13 | 15 | 2.0 | 1.55 | -1.0 | -2.58 | 0.58 |

Note: Here and in Tables 5-9: M, mean value; SD, standard deviation; MD, mean difference; CI, confidence interval

Table 5: Parameters of linear blood flow velocity in prostatic veins according to study data, cm/s

| Study | Experimental group | | | Control group | | | MD | 95 % CI | |
|--------------------------|--------------------|------|------|---------------|------|------|------|-------------|-------------|
| | n | M | SD | n | M | SD | | lower limit | upper limit |
| Ershov E.V. (2007) [25] | 664.92 | 1.54 | | 40 | 3.98 | 1.01 | 0.94 | 0.45 | 1.43 |
| Tkachuk V.N. (2015) [28] | 210 | 4.91 | 4.49 | 40 | 3.12 | 3.23 | 1.79 | 0.62 | 2.96 |

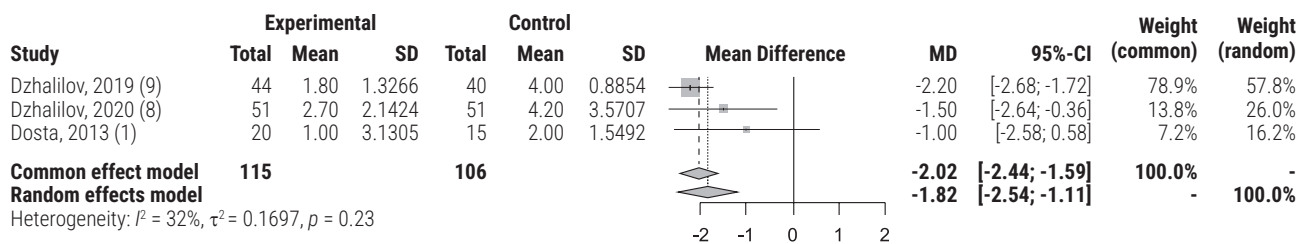


Figure 4: Meta-Analysis of Changes in QOL Score after Treatment

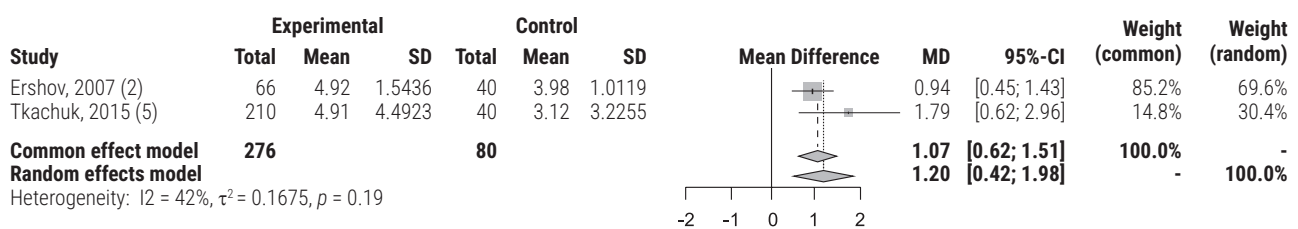


Figure 5: Meta-Analysis of Changes in the Linear Velocity of Blood Flow in the Prostatic Veins After Treatment

Thus, the use of therapy including Wobenzym in patients with CBP significantly increases linear blood flow velocity in prostatic veins by more than 1 cm/s compared to therapy without Wobenzym. Difference in mean values (MD) in the fixed effects model is 1.07 (95% CI 0.62-1.51; $p = 0.00$);

in the random effects model, it is 1.20 (95% CI 0.42-1.68; $p = 0.00$).

3.3 Changes in Peak Systolic Blood Flow Velocity in Prostatic Arteries after Treatment

The above parameter has been provided appropriately in the following articles: Ershov E.V. (2007) [25], Tkachuk V.N. (2007) [29], Tkachuk V.N. (2015) [28] (Table 6).

According to the results obtained, there is no heterogeneity in the data ($I^2 = 0\%$), $\tau^2 = 0.06$, $p > 0.10$. In this case, the 95% CI of the pooled mean difference calculated both for the fixed and random effects models does not overlap the zero value (Figure 6).

Thus, the use of therapy including Wobenzym in patients with CBP significantly increases peak systolic blood flow velocity in the prostatic arteries compared to therapy without Wobenzym. The difference between the groups is 3.5 cm/s,

i.e., in patients taking Wobenzym, the value of peak systolic velocity was almost 30% higher than in controls. Mean difference (MD) in the fixed effects model is 3.48 (95% CI 2.67-4.29; $p = 0.00$); in the random effects model, it is 3.48 (95% CI 2.62-4.34; $p = 0.00$).

3.4 Change In Maximum urine Flow Rate After Treatment

The above parameter has been provided appropriately in the following articles: Kodiri T.R. (2013) [28], Solihov D.N. (2009) [30], Dzhililov H.N. (2019) [31] (Table 7).

The results show no heterogeneity in the data ($I^2 = 0\%$), $\tau^2 = 0.0005$, $p > 0.10$. In this case, the 95% CI of the pooled mean difference calculated for both the fixed and random effects models does not overlap the zero value (Figure 7).

Table 6: Parameters of Peak Systolic Blood Flow Velocity in The Prostatic Arteries According to The Study Data, Cm/S

| Study | Experimental group | | | Control group | | | MD | 95% CI | |
|--------------------------|--------------------|-------|------|---------------|-------|------|------|-------------|-------------|
| | n | M | SD | n | M | SD | | lower limit | upper limit |
| Ershov E.V. (2007) [25] | 66 | 13.92 | 8.62 | 40 | 10.62 | 3.42 | 3.30 | 2.04 | 4.56 |
| Tkachuk V.N. (2007) [29] | 70 | 13.02 | 6.35 | 65 | 10.06 | 6.77 | 2.96 | 1.17 | 4.75 |
| Tkachuk V.N. (2015) [28] | 210 | 14.02 | 5.65 | 40 | 10.06 | 3.42 | 3.96 | 2.65 | 5.27 |

Table 7: Parameters of Maximum Urine Flow Rate According to Study Data

| Study | Experimental group | | | Control group | | | MD | 95% CI | |
|-------------------------------|--------------------|-------|----|---------------|-------|-----|------|-------------|-------------|
| | n | M | SD | n | M | SD | | lower limit | upper limit |
| Dzhililov H.N. 44 (2019) [31] | 19.0 | 8.62 | 40 | 13.1 | 7.59 | 5.9 | 2.43 | 9.37 | |
| Kodiri T.R. (2013) 28 [28] | 19.5 | 6.35 | 40 | 13.2 | 10.75 | 6.3 | 2.22 | 10.38 | |
| Solihov D.N. 70 (2009) [30] | 19.0 | 10.88 | 65 | 13.1 | 9.67 | 5.9 | 2.43 | 9.37 | |

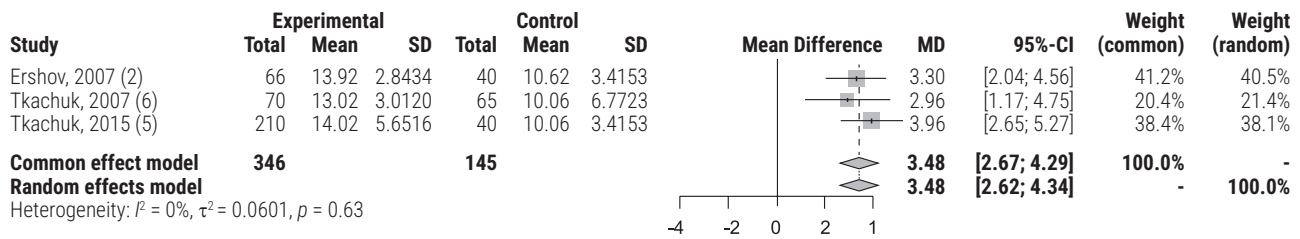


Figure 6: Meta-Analysis of Changes in Peak Systolic Blood Flow Velocity in Prostatic Arteries After Treatment

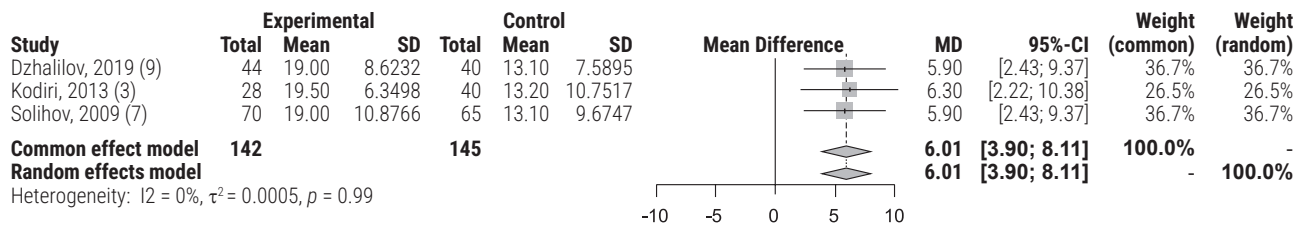


Figure 7: Meta-Analysis of Change in Maximum Urine Flow Rate After Treatment

Thus, the use of therapy including Wobenzym in patients with CBP significantly increases the maximum urine flow rate compared to therapy without Wobenzym. Difference in mean values (*MD*) in the fixed effects model is 6.01 (95% CI 3.9-8.11; $p = 0.00$), in the random effects model is 6.01 (95% CI 3.9-8.11; $p = 0.00$).

3.5 Change in NIH-CPSI "Pain" Subscale Scores after Treatment

The above parameter has been provided appropriately in the following articles: Dosta N.I. (2013) [16], Tkachuk V.N. (2015) [28] (Table 8).

The results show moderate heterogeneity in the data ($I^2 = 66\%$), $\tau^2 = 6.87$, $p = 0.10$. In this case, the 95% CI of the pooled mean difference calculated for both the fixed and random effects models does not overlap the zero value (Figure 8).

Thus, the use of therapy including Wobenzym in patients with CBP significantly reduces the

number of scores of the "Pain" subscale of NIH-CPSI compared to therapy without Wobenzym. The difference between the groups is 5 points. Difference in mean values (*MD*) in the fixed effects model is -5.17 (95% CI -7.33 to -3.0; $p = 0.00$), in the random effects model is -6.60 (95% CI -8.65...-0.76; $p = 0.02$).

3.6 Change in NIH-CPSI "Quality of Life" Subscale Scores after Treatment

The above parameter has been provided appropriately in the following articles: Dosta N.I. (2013) [15], Tkachuk V.N. (2015) [28] (Table 9).

According to the results obtained, there is moderate heterogeneity in the data ($I^2 = 73\%$), $\tau^2 = 1.86$, $p < 0.10$. In this case, the 95% CI of the pooled mean difference calculated for both the fixed model and the.

Table 8: NIH-CPSI "Pain" Subscale Scores According to Research Data

| Study | Experimental group | | | Control group | | | MD | 95 % CI | |
|--------------------------|--------------------|----------|-----------|---------------|----------|-----------|------|-------------|-------------|
| | <i>n</i> | <i>M</i> | <i>SD</i> | <i>n</i> | <i>M</i> | <i>SD</i> | | lower limit | upper limit |
| Dosta N.I. (2013) [16] | 20 | 5.9 | 8.50 | 15 | 8.1 | 3.69 | -2.2 | -6.32 | 1.92 |
| Tkachuk V.N. (2015) [28] | 210 | 2.1 | 7.25 | 60 | 8.6 | 7.59 | -6.3 | -8.85 | -3.75 |

Table 9: NIH-CPSI “Quality of Life” Subscale Scores According to Study Data

| Study | Experimental group | | | Control group | | | MD | 95 % CI | |
|--------------------------|--------------------|-----|------|---------------|-----|------|------|-------------|-------------|
| | n | M | SD | n | M | SD | | lower limit | upper limit |
| Dosta N.I. (2013) [15] | 20 | 2.0 | 6.02 | 15 | 3.0 | 1.96 | -1.0 | -3.02 | 1.02 |
| Tkachuk V.N. (2015) [28] | 210 | 3.1 | 5.80 | 60 | 6.5 | 3.79 | -3.6 | -6.81 | -1.99 |

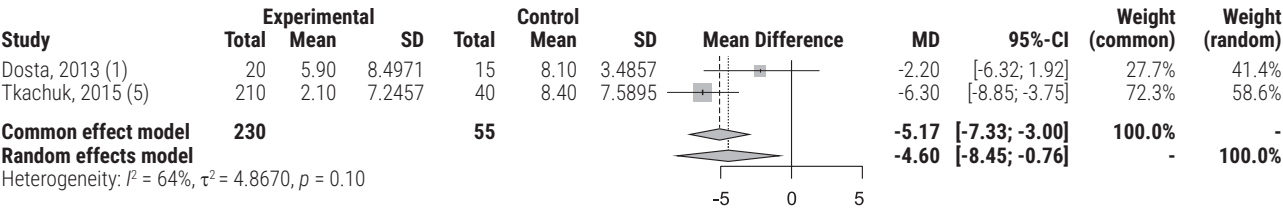


Figure 8: Meta-Analysis of Change in NIH-CPSI “Pain” Subscale Scores after Treatment

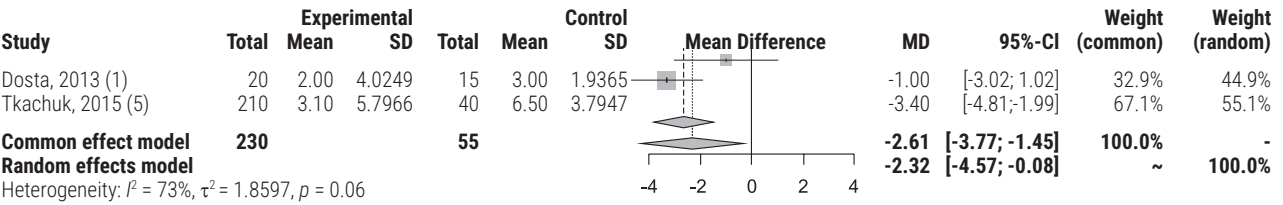


Figure 9: Meta-Analysis of Change in NIH-CPSI “Quality of Life” Subscale Scores after Treatment

Table 10: Immunogram Parameters in Patients according to the Study by N.Yu. Noskov (2004) [27]

| Immunologic parameters | Before treatment | After treatment | | | |
|--|------------------|--------------------|---------------|-------------|-------|
| | | Experimental group | Control group | | |
| | | M±SD | P | M±SD | P |
| CD3 ⁺ -lymphocytes, % | 82.9 ±9.4 | 69.4 ±8.8 | <0.01 | 79.5 ±10.1 | 0.1 |
| CD4 ⁺ -lymphocytes, % | 24.1 ±3.8 | 41.6 ±8.8 | <0.01 | 35.4 ±7.1 | <0.05 |
| CD8 ⁺ -lymphocytes, % | 18.1 ±2.4 | 24.8 ± 3.5 | <0.01 | 20.5 ±1.7 | <0.05 |
| CD22 ⁺ -lymphocytes, % | 14.3 ±0.9 | 23.6 ±2.4 | <0.01 | 19.4 ±3.3 | <0.05 |
| PHA-induced lymphocyte activity, imp/min | 4310 ±106 | 7231 ±80 | <0.01 | 4935 ±215 | <0.05 |
| Level of complement CH-100, arbitrary units. | 98.5 ±5.3 | 169.8 ±8.4 | <0.01 | 109.1 ±5.1 | <0.05 |
| Circulating immune complexes, arbitrary units. | 0.05 ±0.008 | 0.07 ±0.005 | <0.05 | 0.06 ±0.009 | <0.05 |
| CD4/CD8, arbitrary units. | 1.33 ± 0.3 | 1.68 ±0.5 | <0.01 | 1.73 ±0.4 | <0.01 |
| IgM, g/L | 0.5 ±0.1 | 0.9 ±0.3 | <0.01 | 0.6 ±0.3 | <0.05 |
| IgG, g/L | 6.0 ±0.4 | 10.3 ±0.4 | <0.01 | 8.3 ±1.1 | <0.05 |
| IgA, g/L | 2.2 ±0.6 | 3.4 ±0.7 | <0.01 | 2.6 ±0.5 | <0.05 |

Note. M, average value; SD, standard deviation; MD, mean difference; CI, confidence interval; PHA, phytohemagglutinin. of the random effects model, does not cross the zero value (Fig. 9).

Thus, the use of therapy including Wobenzym in number of scores of the subscale "Quality of Life" patients with CBP significantly reduces the of NIH-CPSI compared to therapy without

Wobenzym. The difference between the groups is 2 points. Difference in mean values (*MD*) in the fixed effects model is -2.61 (95% CI -3.77...-1.45; $p = 0.00$), in the random effects model is -2.32 (95% CI -4.57...-0.08; $p = 0.04$).

3.7 Change in Immunogram Parameters after Treatment

This parameter was provided appropriately only in the article by Noskov N.Yu. (2004) [27] (Table 10).

After the treatment, significant improvement of immunogram parameters was found in both groups. However, a greater increase in the number of CD4⁺ was noted in the experimental group, DOI: <https://doi.org/10.17816/uroved.626639> CD8⁺-lymphocytes, lymphocyte activity, complement CH-100 level and immunoglobulins M, G, A [29].

The study by V.N. Tkachuk et al. (2015) [28] also provided the findings of an immunologic study. In the experimental group, where complex treatment included Wobenzym, the improvement of all immunologic indices occurred significantly earlier. Before treatment, immunodeficiency states characterized by impaired T-cell immunity and decreased functional activity of phagocytes were revealed in patients with CBP. After treatment, the patients in the experimental group showed an increase in the number of T-lymphocytes with CD3⁺ phenotype from 35.6 ± 2.9 to 49.3 ± 2.7 % ($p < 0.01$), the number of T-cells with CD4⁺ phenotype from 17.9 ± 2.1 to 32.4 ± 1.9 % ($p < 0.01$), B-lymphocytes (CD22⁺) from 14.3 ± 0.9 to 20.5 ± 1.8 % ($p < 0.01$) ($p < 0.05$), the ratio of T-helper and T-suppressors increased from 1.1 ± 0.1 to 1.7 ± 0.3 ($p < 0.05$) and functional activity of lymphocytes increased from 4338 ± 209 to 7396 ± 346 imp/min ($p < 0.001$).

IV. FINDINGS

We found 9 non-randomized clinical trials on the efficacy of combined therapy including Wobenzym in patients with CBP compared with standard therapy without Wobenzym. Meta-analysis showed that:

1. Most researchers in their works have shown that the use of therapy including Wobenzym in patients with CBP significantly more often leads to eradication of the pathogen compared to therapy without Wobenzym. The OR in the fixed effects model is 11.19 (95% CI 6.42-19.50; $p = 0$), while in the random effects model, it is 11.22 (95% CI 5.75-21.88; $p = 0$).
2. Therapy including Wobenzym in patients with CBP significantly reduces QoL scores compared to therapy without Wobenzym. The study demonstrated significant difference of 2 points between the groups. *MD* in the fixed effects model is -2.02 (95% CI -2.44 to -1.59; $p = 0$), while in the random effects model, it is -1.82 (95% CI -2.54..-1.11; $p = 0$).
3. Therapy including Wobenzym in patients with CBP significantly increases linear blood flow velocity in prostatic veins by more than 1 cm/s compared to therapy without Wobenzym. Studies have demonstrated significantly improved blood flow in the prostate gland. *MD* in the fixed effects model is 1.07 (95% CI 0.62-1.51; $p = 0$), while in the random effects model, it is 1.20 (95% CI 0.62-1.68; $p = 0$). The result is valid, indicating significant difference between groups.
4. Therapy including Wobenzym in patients with CBP significantly increases peak systolic blood flow velocity in prostatic arteries compared to therapy without Wobenzym. The difference between the groups is 3.5 cm/s. *MD* in the fixed effects model is 3.68 (95% CI 2.67-6.29; $p = 0.00$), while in the random effects model, it is 3.68 (95% CI 2.62-6.36; $p = 0.00$).
5. Therapy including Wobenzym in patients with CBP significantly increases the maximum urine flow rate compared to therapy without Wobenzym. *MD* in the fixed effects model is 6.01 (95% CI 3.9-8.11; $p = 0.00$), while in the random effects model, it is 6.01 (95% CI 3.9-8.11; $p = 0.00$);
6. Therapy including Wobenzym in patients with CBP significantly reduces the number of scores of the NIH-CPSI "Pain" subscale compared to therapy without Wobenzym. The difference between the groups is 5 points. *MD* in the fixed effects model is -5.17 (95% CI -7.33 to -3.0; $p = 0.00$), while in the random

effects model, it is -4.60 (95% CI -8.45...-0.76; $p = 0.02$);

7. Therapy including Wobenzym in patients with CBP significantly reduces the scores of the NIH-CPSI "Quality of Life" subscale compared to therapy without Wobenzym. The result is statistically valid, but there is high heterogeneity in the data. The difference between the groups is 2 points. The high heterogeneity is explained by the small number of included studies. MD in the fixed effects model is -2.61 (95% CI -3.77 to -1.45 $p = 0.00$), while in the random effects model, it is 2.32 (95% CI -4.57...-0.08; $p = 0.04$);
8. Therapy including Wobenzym in patients with CBP leads to a greater increase in $CD4^{+}$ -, $CD8^{+}$ - lymphocyte counts, lymphocyte functional activity, CH-100 complement levels and immunoglobulins M, G, A.

4.1 Overall Completeness and Applicability of Evidence

All studies used the similar regimen of Wobenzym therapy and comparable duration of courses. The age of the study participants ranged widely (from young to old), allowing the results obtained in the studies to be extrapolated to the population receiving Wobenzym in real practice.

4.2 Quality of Evidence

We did not rate any of the studies as being at high risk of bias in all areas. For most areas of risk of bias, the risk was rated as "unclear".

4.3 Risk of Bias During Tte Review

We performed the data extraction without any constraints.

4.4 Consistency and Disagreement with Other Studies and Reviews

We found no other systematic reviews of the efficacy of Wobenzym in the complex therapy of CBP in open sources.

4.5 Commercial Impact

No conflicts of interest were declared in any of the studies.

V. CONCLUSION

A systematic review/meta-analysis found evidence of the beneficial effects of including Wobenzym in the complex therapy of CBP. Complex therapy including Wobenzym, compared to therapy without Wobenzym, increases the frequency of pathogen eradication by 11 times, which is important for the treatment of infectious and inflammatory processes in the prostate gland and is associated with pathogenetic anti-inflammatory effect, DOI <https://doi.org/10.17816/uroved626639>. antibiofilm effect of the drug and its influence on the mobility and adhesion of the pathogen. In addition, complex therapy with Wobenzym improves blood supply of the prostate gland, as evidenced by the improvement of microcirculation in the arterial and venous bed of the prostate tissue, which is probably due to the positive effect of the drug on the course of the inflammatory process, on the change, improvement of rheological properties of blood and vascular-thrombocyte homeostasis.

Inclusion of the Wobenzym in the therapy of chronic prostatitis contributes to an increase in the maximum rate of urine flow, improved urination, which is due to a decrease in edema of the prostate tissue. Therapy with Wobenzym reduces the severity of prostatitis symptoms, which is confirmed by a decrease in the number of scores on the "Pain" subscale and a decrease in the number of scores on the "Quality of Life" subscale of the NIH-CPSI and the QoL scale. These data indicate the control/reduction of symptoms of the disease and improvement of the quality of life of patients with CBP in the study group.

Inclusion of Wobenzym in the therapy of chronic prostatitis stimulates immune defense, which is confirmed by a large increase in $CD4^{+}$ -, $Co8^{+}$ -lymphocytes, functional activity of lymphocytes, the level of complement CH-100 and immunoglobulins M, G, A in comparison with the group of patients in whose treatment Wobenzym was not used.

Taking into account the above-mentioned, evident statistically reliable, positive effect of Wobenzym

in complex therapy of patients with CBP is due to its pathogenetic orientation in relation to this group of patients.

In order to form an evidence base and obtain more reliable results, it is recommended to conduct randomized blinded trials with similar endpoints and timing of their control in groups of patients with CBP.

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Neurocognitive Effects of Alcohol in the Elderly with Dementia

Dr. Pieroni Cavaglier

ABSTRACT

In Brazil, it is estimated that 2 million people live with dementia syndromes, with a tendency to triple by 2050, according to the Global Burden of Disease. At the same time, Vigitel found that 20.8% of the population will consume alcohol excessively in 2023. In view of this, elucidating the relationship between alcohol and dementia in the elderly is relevant. This study aims to assess the relationship between alcohol consumption throughout life and the impact on neurocognition in the elderly. Using the descriptors "aged", "dementia" and "ethanol" with the operator AND in the PubMed, VHL and Cochrane databases, associated with the inclusion criteria of publication in the last 20 years, availability in full and English, Portuguese or Spanish language, 9 studies were selected, after excluding duplicates and analyzing titles and abstracts.

Keywords: ethanol, dementia, aged.

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Neurocognitive Effects of Alcohol in the Elderly with Dementia

Neurocognitive Effects of Alcohol in Elderly Individuals with Dementia

Neurocognitive Effects of Alcohol in Elderly People with Dementia

Dr. Pieroni Cavagliar

SUMMARY

In Brazil, it is estimated that 2 million people live with dementia syndromes, with a tendency to triple by 2050, according to the Global Burden of Disease. At the same time, Vigitel found that 20.8% of the population will consume alcohol excessively in 2023. In view of this, it is important to elucidate the relationship between alcohol and dementia in the elderly. This study aims to assess the relationship between alcohol consumption throughout life and the impact on neurocognition in the elderly. Using the descriptors "aged", "dementia" and "ethanol" with the operator AND in the PubMed, VHL and Cochrane databases, associated with the inclusion criteria of publication in the last 20 years, availability in full and English, Portuguese or Spanish language, 9 studies were selected, after excluding duplicates and analyzing titles and abstracts. Of the studies reviewed, 4 found an association between light to moderate alcohol consumption and a lower risk of developing and progressing dementia, while 2 had inconclusive findings. With regard to high consumption, 3 studies found no statistically significant relationship with dementia, and 4 associated this amount of alcohol with a higher risk of developing and progressing the condition. This review suggests that light to moderate alcohol consumption may be associated with a lower likelihood of developing or progressing to dementia, while findings on the effects of high consumption are divergent, yet most recent evidence points to the pathological role of this amount of alcohol consumption on cognition. The need for more

research is highlighted, especially with samples from the Brazilian population, since none of the studies found were Brazilian.

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SUMMARY

In Brazil, it is estimated that 2 million people live with dementia syndromes, with a tendency to triple by 2050, according to the Global Burden of Disease. At the same time, Vigitel found that 20.8% of the population will consume alcohol in excess in 2023. In view of this, it is important to clarify the relationship between alcohol and dementia in the elderly. This study aims to assess the relationship between alcohol consumption throughout life and the impact on neurocognition in the elderly. Using the descriptors "aged", "dementia" and "ethanol" with the operator AND in the PubMed, VHL and Cochrane databases, associated with the inclusion criteria of publication in the last 20 years, availability in its entirety and English, Portuguese or Spanish language, 9 studies were selected, after excluding duplicates and analyzing titles and abstracts. Of the studies reviewed, 4 found an association between light to moderate alcohol consumption and a lower risk of developing and progressing dementia, while 2 had inconclusive results. With regard to excessive alcohol consumption, 3 studies did not find a statistically significant relationship with dementia, while 4 associated this amount of alcohol with a higher risk of developing and progressing the disease. This review suggests that light to moderate alcohol consumption may be associated with a lower likelihood of developing dementia or progressing to it, while the findings on the effects of high consumption are divergent, although the most recent evidence points to the pathological role of this level of alcohol consumption on cognition. There is a need for further research, especially with samples of the Brazilian population, since none of the studies found were Brazilian.

Palabras clave: alcohol, dementia, elderly people.

I. INTRODUCTION

Dementia is a clinical syndrome characterized by the progressive decline of cognitive functions, affecting memory, language, executive functions, abstraction, judgment and other essential skills for everyday life (12).

In Brazil, it is estimated that around 2 million people live with some form of dementia, while in the world, this figure rises to 55 million, and the WHO estimates that by 2050, there will be 139 million people living with this syndrome (9). In this context, ReNaDe 2023 (3), a Brazilian report on dementias, reiterates the importance of the issue and provides new information on the Brazilian context. This report indicates that only 20% of dementia cases in Brazil are properly diagnosed, which is a challenge even for wealthier countries, and may be related to factors such as: lack of knowledge among the general population, lack of training on the subject among health professionals and lack of existing services that adequately meet the needs of people with dementia and their caregivers.

At the same time, excessive alcohol consumption was found in 18.4% of the Brazilian population in 2021 by Vigitel, with a dose of alcohol considered to be 14g of pure ethanol, and alcohol abuse from 4 doses on the same occasion for women and 5 for men. In addition, the Vigitel 2023 report shows a worrying increase in alcohol abuse in Brazil, especially among women. In the general population, the rate rose from 18.4% to 20.8% between 2021 and 2023. Among men, the increase was from 25% to 27.3%, while among women, the increase was even greater, from 12.7% to 15.2%. Comparing 2023 with 2010, there is a significant increase in abusive consumption among women, while among men there is a more stable scenario. This growth among women is mainly responsible for the general increase in consumption over the period and deserves special attention (4).

The 2022 Demographic Census showed a significant increase in the Brazilian population

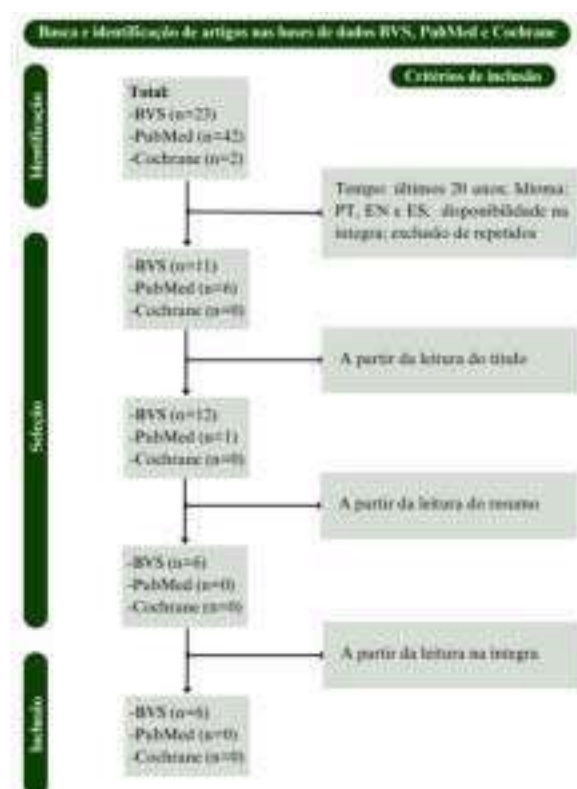
aged 65 and over, equivalent to 10.9% of the country's total population, corresponding to an increase of 57.4% compared to 2010 (2). This change, driven by a fall in fertility and an increase in life expectancy, has transformed the country's age pyramid, with fewer children and young people and more adults and elderly people. This increase has been observed more rapidly in the South and Southeast regions of the country (2).

In this context, elucidating the relationship between alcohol and dementia in the elderly is a highly relevant issue for public health. Therefore, the question to be clarified is whether alcohol consumption throughout life is a predisposing factor and/or a worse prognosis for dementia in the elderly population, whether by increasing, reducing or not interfering in the development of the disease.

In short, the aim of the study was to assess the relationship between alcohol consumption throughout life and its impact on neurocognition in the elderly.

II. METHODOLOGY

A literature review was carried out on January 28, 2024, using the descriptors "Aged", "Dementia" and "Ethanol" with the Boolean operator AND in the PubMed, VHL and Cochrane databases, resulting in 67 articles. The inclusion criteria adopted were publication in the last 20 years, availability in full and the language being English, Portuguese or Spanish, and after excluding duplicates, 17 publications remained. After analyzing the titles and abstracts, 6 studies were selected that were appropriate to the topic. Three articles used in the Mewton et. al (2022) meta-analysis, found by the previously described research, were subsequently added to the review.



Source: Prepared by the authors

Figure 1: Flowchart of the Methodology

III. RESULTS AND DISCUSSION

3.1 Results on Light to Moderate Alcohol Consumption

Table 1: Summary of Findings on Light to Moderate Alcohol Consumption

| Light to Moderate Alcohol Consumption | | |
|--|--|------------------------|
| Relation to increased risk of developing or progressing dementia | Lower risk of developing or progressing dementia | Inconclusive findings |
| | Mewton et. al (2022) | Topiwala et. al (2018) |
| | Liu Y, et. al (2019) | Rao et. al (2015) |
| | Solfrizzi et. al (2007) | |
| | Ilomaki, J et. al (2015) | |

Source: Prepared by the Authors

Among the studies analyzed, regarding the amount of alcohol associated with protective or harmful effects on the nervous system, MEWTON, L. et. Al (2022) pointed out that in dose-response analyses, moderate consumption of up to 40 g/day was associated with a lower risk of all-cause dementia when compared with lifelong abstinence as well as in former drinkers. Among current drinkers in the general population, there was no consistent evidence to suggest that the amount of alcohol consumed later in life was significantly associated with the risk of dementia. This study does not provide evidence on the relationship between the risk of dementia and excessive alcohol consumption or alcohol use disorders, which are relatively rare in the general population. The results on the alcohol-dementia relationship were similar when the sample was stratified by sex but showed substantial heterogeneity when analyzed at the continental level.

SOLFRIZZI V. et. Al (2007) states that patients with mild cognitive impairment who consumed alcohol in moderate amounts (less than 15g of alcohol/day) had a slower progression to dementia than those who did not consume alcohol, yet patients whose moderate consumption was specifically wine (1 glass/day) had an even slower progression to dementia.

There was no statistically significant relationship between high alcohol consumption (>15g of alcohol/day) and the rate of progression to dementia when comparing patients who did not consume alcohol and those who consumed alcohol moderately. The level of alcohol consumption also had no relevant relationship with the incidence of mild cognitive impairment.

LIU, Y. et. Al (2019) states that the association between alcohol consumption and dementia syndromes showed that the difference between occasional and daily alcohol consumption was statistically significant in men (1.12, 95% CI 1.02-1.23), but not in women (0.97, 95% CI 0.85-1.10). Relative risk values remained significantly lower in men and women with alcohol consumption ≤ 2 units/day, occasionally, as well as daily. No significant association was observed in either sex for alcohol consumption >2 units/day, occasionally or daily.

In agreement, ILOMAKI, J et. al (2015) found in a systematic review, in which 45 studies on light to moderate consumption were incorporated, a reduced risk of dementia compared to not drinking. There was no clear risk in light or moderate consumption, nor was the study population separated into men and women. What was found was that drinking less than 21 units of alcohol per week (where 1 unit of alcohol = 10 mL

or 8 g of pure alcohol) may be associated with a lower risk of dementia.

TOPIWALA, A. et. Al (2018) found that the information related to moderate consumption

was conflicting, and the reason given by the authors themselves for this finding was that the definition of "moderate consumption" varied greatly between studies.

3.2 Results on High Alcohol Consumption

Table 2: Summary of Findings on High Alcohol Consumption

| High Alcohol Consumption | | |
|--|---|-----------------------|
| Relation to increased risk of developing or progressing dementia | No significant impact on the development or progression of dementia | Inconclusive findings |
| Topiwala et. al (2018) | Aho L et. al (2009) | |
| Rao et. al (2015) | Liu Y, et. al (2019) | |
| Livingston et. al (2020) | Solfrizzi et. al (2007) | |
| Piumatti, G et. al (2018) | | |

Source: Prepared by the Author

As for the prevalence of the onset of dementia among alcohol consumers, according to TOPIWALA, A. et. Al (2018) , it was found that the data found regarding chronic and heavy alcohol consumption reached the same or very similar conclusions among the studies reviewed, highlighting the increased risk of developing dementia and cognitive decline and the establishment of various damages to brain structures.

RAO, R. et al. (2015) found that alcohol misuse complicates primary dementia by increasing cognitive decline, caused by neurotoxicity or stroke. This study also found that individuals with brain damage due to alcohol misuse perform less well in visuospatial activities when compared to people with other neurological disorders. However, the exact amount of alcohol consumption that triggers the onset of brain damage in older people has not been determined, and there is a higher prevalence of studies involving younger people compared to those using older people as a sample. Another counterpoint is that the commonly used diagnostic test (Mini Mental Examination) for amnesic syndromes does not assess the function

of the frontal lobe, which is more susceptible to the long term effects of excessive alcohol consumption, nor the impaired consolidation of long term memories in this type of comorbidity.

In contrast to the above, AHO, L. et. Al (2009) demonstrated a higher prevalence of both micro and macroscopic neurological lesions in patients with ACA (high alcohol consumption). It was also found that in 34% of ACA samples, type II Alzheimer's astrocytes were present in the putamen and severe white matter rarefaction.

However, there was no significant difference between the groups and genders in terms of beta amyloid aggregation or vascular lesions. In short, there was no statistically significant influence of alcohol in the post-mortem samples, suggesting that the relationship between alcohol and dementia has a different pathogenesis from the most common degenerative disorders. It was also concluded that chronic and severe alcohol consumption has no influence on the production or accumulation of B-amyloid protein, nor is it related to the hyperphosphorylation of Tau protein. However, the control group also included patients who consumed alcohol lightly, so it was

not possible to study the effects of moderate consumption on the brain.

Other studies researched beyond the search of the databases used also revealed contradictory results. According to LIVINGSTON et. Al (2020), a French longitudinal study, with a 5-year follow-up and a study population of around 31 million people admitted to hospital, concluded that alcohol consumption disorders (harmful consumption or dependence, as defined in the ICD) were associated with an increased risk of dementia. During the study stages, specific analyses were carried out for men and women (women HR 33, 95% CI 33-34, men 34, 33-34), where the association between dementia and alcohol use disorders was found, and was specifically notable in early onset dementias (age under 65), where 56.6% had an alcohol use disorder noted in their records (n=57,353; 5.2% all dementias).

Corroborating the excerpt above, PIUMATTI, G. et. Al (2018) carried out a 5-year follow-up of 13,342 men and women volunteers from the UK biobank aged between 40 and 73 who consumed alcohol, in which it was found that those who drank more than 12 doses of alcohol per week decreased their reaction time slightly more in a perceptual matching task than those who drank less, however, few heavy drinkers were included and abstainers were not analyzed. Piumatti et. al also points out that, in another study in Whitehall in the UK, with 23 years of follow-up, in which 9,087 participants aged between 35 and 55 were observed at the start of the study, it was seen that drinking more than 21 units a week was associated with a 17% increase in dementia compared to drinking less than 14 units, to the point that consuming more than 14 units also showed a correlation with atrophy of the right hippocampus in the MRI procedure.

IV. CONCLUSION

This review found data supporting the hypothesis that there is a relationship between light to moderate alcohol consumption throughout life and a lower probability of developing or progressing dementia syndromes. On the other

hand, the findings about high consumption being related to a worse prognosis differed, so that evidence suggesting alcohol as an etiological element of dementia ended up coexisting with studies that found no significant relationship between high consumption of this substance and cognitive worsening. Even so, the evidence pointing to the pathological role of alcohol consumption is greater and more recent, so that the hypothesis of a deleterious relationship between alcohol and cognitive ability becomes more robust and probable.

A barrier was found regarding the amount of alcohol in grams that would be related to a better or worse prognosis of dementia syndromes, since no study has been able to quantify the exact threshold at which alcohol loses its possible protective factor and becomes pathogenic. The limited availability of literature and the inconclusiveness of some of the findings highlight the need for more research in this area, especially those aimed at using the Brazilian population as a sample, since none of the studies found were Brazilian.

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Risks of Endometrial Carcinogenesis and Assisted Reproductive Technologies: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose of Study: to study the possible relationship between in vitro fertilization, the use of ovulation stimulation drugs and the risk of developing uterine cancer in women with infertility.

Material and Methods: literature search for a systematic review was carried out in the bibliographic databases Medline, ClinicalKey, Google Scholar, Embase, The Cochrane Library, eLIBRARY for the period 1999-2022. Publications were searched using keywords defined according to the PICO principle (P = population or patients, I = intervention, C = comparison and O = outcomes): female, women, infertility, infertility treatment, in vitro fertilization, IVF, assisted reproductive technologies, ART, ovarian stimulation, ovarian hyperstimulation, clomiphene citrate, hCG, hMG, tamoxifen, uterine, endometrial, cancer, carcinoma neoplasm, uterine neoplasms. The following SQL operators were used during the search: AND, OR.

Keywords: uterine cancer, infertility, ovulation induction, in vitro fertilization, meta-analysis.

Classification: NLM Code: WJ190, WP570, WP570.5

Language: English



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Results: As a result of the search, 37 representative publications were found, during the selection process 8 studies were selected for meta-analysis.

Conclusion: A systematic review and meta-analysis has demonstrated the ambiguity of the design and results of studies on the possible relationship of uterine cancer and methods of assisted reproductive technologies published to date. The problem is very relevant due to the high incidence of infertility and the increase in the incidence of cancer of the female reproductive organs. The conducted studies confirm the impossibility to evaluate in isolation the carcinogenic effect of ovulation inducers or in

vitro fertilization methods without adjusting for the infertility factor, as well as risk factors for uterine cancer. There remains a high need for more research as well as for the safety profile of infertility treatments in relation to long-term cancer risks.

Keywords: uterine cancer, infertility, ovulation induction, in vitro fertilization, meta-analysis.

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I. INTRODUCTION

In recent years, infertility has become one of the most important problems affecting young couples around the world [1]. In our country, the incidence of infertility in marriages ranges from 17.2% - 24%, depending on the region [2-5]. In 25.2% - 42.3%, the cause of infertility is uterine factor. In the structure of diseases of this group in Russia, chronic endometritis prevails, its prevalence is 2 times higher than that of other pathologies, and in patients with unsuccessful attempts at in vitro fertilization (IVF), its frequency is the highest (52-67.7%) [6]. Almost 10% of the population or one in seven couples in developed countries face difficulties in conceiving naturally and are forced to resort to infertility treatment methods using assisted reproductive technologies (ART) [1, 7-9]. Since 1995, the National Register of ART results has been maintained in Russia, according to which in 2003, 1830 children were born through ART (0.12% of all births), in 2011 - 14,533 children (0.81% of all births), in 2014 - 24,707 children (1.27% of all births); in 2015 - 30,039 children (1.5% of all

births) [6]. By 2017, there had been more than 160,000 such children in Russia, and their number is steadily growing [10]. Worldwide, the number of children born with the help of assisted reproductive technologies reaches seven million [11]. The main factor contributing to this growth is the postponement of childbearing due to the desire for a successful career and other socio-economic factors, such as the financial and educational level of people trying to conceive [1, 12-13].

As a result of studying the dynamics of detection of uterine corpus cancer (UCC) in Russia, the following was found: in the period 1991 – 2007, the absolute number of newly diagnosed cases increased from 11,300 to 18,300 cases, and the proportion in the incidence structure increased from 5.8% to 7.1% [14]. In the dynamics of subsequent years (2007-2017), the incidence of UCC increased from 24 per 100,000 to 33.1 per 100,000 women. According to 2017 data, uterine cancer is in third place (7.8%) [15]. From the very beginning of the use of ART, there has been constant discussion among the scientific community about the long-term effects of infertility treatment and, mainly, about their potential impact on the subsequent risk of developing cancer [12-13].

Many of the etiological factors in the development of reduced fertility, such as genetic predisposition, environmental, physiological factors, as well as obesity, excessive smoking, anovulation, endometriosis, and the absence of childbirth, in addition to showing a confident trend towards spread, are also independent factors of carcinogenesis [1, 16]. Moreover, it is known that assisted reproductive technologies also involve the use of pharmacological drugs and procedures that have a damaging effect on the main hormone-producing organ - the ovaries. Such trauma during oocyte retrieval and induction of ovulation leads to an increase in the level of sex hormones such as estrogen, progesterone and gonadotropins [1, 8]. The role of hormonal status in the development of malignant neoplasms of the female reproductive system described in the literature suggests an assessment of the

significance of this factor as an integral part of assisted reproductive technologies [7]. Thus, in view of the increase in the prevalence of oncological diseases of the female reproductive system around the world, as well as the global scale of the problem of reduced fertility, it is extremely relevant today to study the possible relationship between various ART methods and the development of oncological diseases in women [17].

II. PURPOSE OF STUDY

To evaluate the existence and nature of the association between infertility treatment, including in vitro fertilization and ovulation inducers used, and the development of endometrial cancer through a systematic review and meta-analysis of retrospective studies.

III. MATERIALS AND METHODS

The review was written according to the PRISMA checklist.

This work was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles. Literature search was carried out in the bibliographic databases Medline, ClinicalKey, Google Scholar, Embase, The Cochrane Library, eLIBRARY. The estimated publication period covered 24 years (1999-2022). Publications were searched using keywords defined in accordance with the PICO principle (P - population or patients, I - intervention, C - comparison and O - outcomes): female, women, infertility, infertility treatment, in vitro fertilization, IVF, assisted reproductive technologies, ART, ovarian stimulation, ovarian hyperstimulation, clomiphene citrate, hCG, hMG, tamoxifen, uterine, endometrial, cancer, carcinoma neoplasm, uterine neoplasms. The following SQL operators were used during the search: AND, OR. The search was based on the titles and texts of the works. Among the works found, the "related articles" tool was used, as well as the analysis of bibliographic references of related works. According to the search algorithm, 37 representative publications were found during the

reporting period and 8 studies were selected for meta-analysis during the selection process (Fig. 1).

The review included all comparative studies of groups with and without in vitro fertilization. Works that did not contain data on the development of malignant neoplasms of the uterine body were excluded from the study; data on the development of malignant processes of other localizations, including the cervix, were also excluded.

Data extraction was performed according to the following structure: year of publication, first author's initials, study design, study groups, cancer rate. Information from the studies, if available, was also extracted and evaluated pertaining to parity (parous / nulliparous), IVF features: number of cycles, ovulation induction.

The main outcome assessed was the development of cancer of the body of the uterus, endometrium in groups with and without IVF.

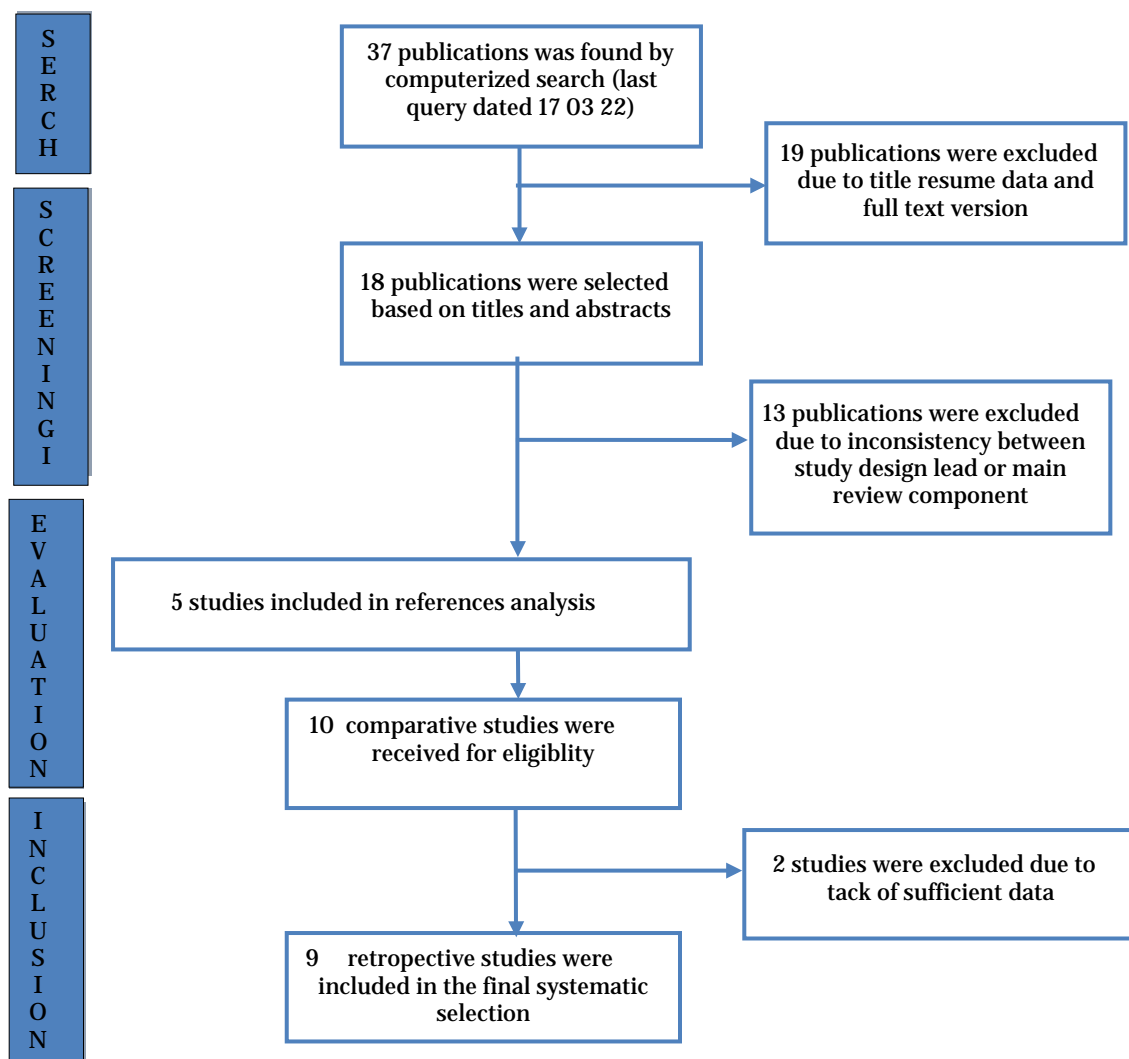


Fig. 1: Methodology for Searching and Selecting Studies for Meta-Analysis

III. RESULTS

Most of the studies examining the risk of developing endometrial cancer in the IVF group of females did not find a significant increase in risk [18-24]. For example, Brinton L.A. et al. report no association between fertility treatment and

endometrial cancer risk (relative risk, $RR = 1.25$, 95% confidence interval, $CI (0.55-2.84)$). Subgroup analysis revealed a slight increase in this risk in the cohort of patients with 1-3 IVF cycles ($RR = 1.94$, 95% $CI (0.73-5.12)$). Moreover, there were no significant associations for the risk of EC development due to the use of a

gonadotropin-releasing hormone analogue (GnRH) (RR = 1.39, 95% CI (0.54–3.55)), clomiphene (RR = 1.01, 95 % CI (0.42–2.42)) or progestogen (RR = 1.24, 95% CI (0.53–2.87)) [18]. Similar conclusions were reached by Kristiansson P. et al., who, when comparing groups of patients with and without IVF (647,704 females), assessed the carcinogenesis of the organs of the female reproductive system and mammary glands of patients in the aggregate, and also presented data on the development of malignant tumors of the uterine body. They summarized that, in accordance with the results, it is impossible declare a significant increase in the risk of developing malignant neoplasms, including the endometrium, in postmenopausal women who gave birth using IVF [19].

Williams C.L. et al. present follow-up data (mean 8.8 years) of 255,786 women who underwent in vitro manipulations with human oocytes, spermatozoa or embryos in order to achieve reproductive function. In a subgroup of patients with malignant tumors of the uterine body, their morphological characteristics were determined in 92% as epithelial, and in 70% as endometrioid. The authors concluded that the risk of developing uterine cancer is not increased compared to the calculated expected value for this population (standardized incidence rate (SIR) - 1.12, 95% CI (0.95 - 1.30)). However, an increased risk of cancer of this localization is associated with ovulation disorders, while multiple births, on the contrary, significantly reduce this risk. In this study, the number of IVF cycles did not show a significant correlation with the risk of developing uterine carcinoma, as well as age at the time of using the ART method and long-term consequences [20]. Yli-Kuha, A.N. et al. report 4 and 2 cases of uterine cancer among 9175 patients in the IVF group and 9175 patients in the control group, respectively, which also indicates the absence of a significant association [24].

Reigstad M.M. et al. conducted a study among 1,353,724 patients included in this study, showed that the risk of endometrial cancer was slightly increased in women who had a history of childbirth and underwent ART in the volume of controlled ovarian hyperstimulation with a

further IVF procedure, which, however, was not supported by statistically significant results (1.62; 95% CI (0.70 - 3.85)). There was no increased risk among women with no history of delivery (0.39; 95% CI (0.15 - 1.03)). The protocols for controlled ovarian hyperstimulation in the patients of this study varied markedly, but mainly included the following three drugs: GnRH analogs (agonists or antagonists), gonadotropins (follicle-stimulating hormone or human menopausal gonadotropin), and human chorionic gonadotropin (hCG). The results of the study also demonstrate that the risk of endometrial cancer is increased in women receiving clomiphene citrate (2.91; 95% CI (1.87 - 4.53)), while the risk level peaked in nulliparous women (4.49; 95 % CI (2.66-7.60)) (p = 0.04). In the group of women who had childbirth, with more than 6 cycles of ovulation stimulation (4.68; 95% CI (1.74 - 12.6)) the statistical significance of the risk was especially high [12]. At the same time, according to Kessous, R. et al., in patients with a history of IVF, the incidence of ovarian and uterine cancer was significantly higher compared to patients in the ovarian stimulation group or without infertility treatment at all [25].

IV. META-ANALYSIS

The meta-analysis of studies was conducted on three outcome measures depending on the study design: 1) the incidence of uterine cancer in the IVF and non-IVF groups 2) the standardized incidence rate (SIR) of uterine cancer in the IVF group 3) the hazard ratio score (HR) development of endometrial cancer in the IVF group.

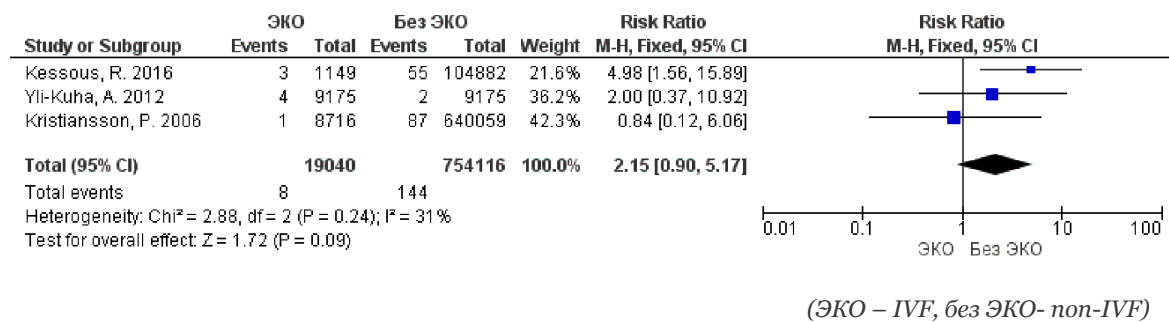


Fig. 2: Tree Diagram. Comparative Analysis of the Incidence Of Uterine Cancer In The Ivf Group And The Group Without Ivf In Studies 1999-2022

In total, according to the pooled data from all three studies (Fig. 2), the incidence of uterine cancer was 0.04% (8 out of 19040) in the IVF group and 0.19% (144 out of 754116) in the non-IVF group. In accordance with the Cochran Q-test, the data are homogeneous ($p > 1$), the I^2 indicator shows a moderate degree of

heterogeneity. Based on the data, a fixed effect model is used. According to the results, in general, there were no statistically significant differences in the incidence of uterine cancer in both groups - RR 2.15 [0.90, 5.17].

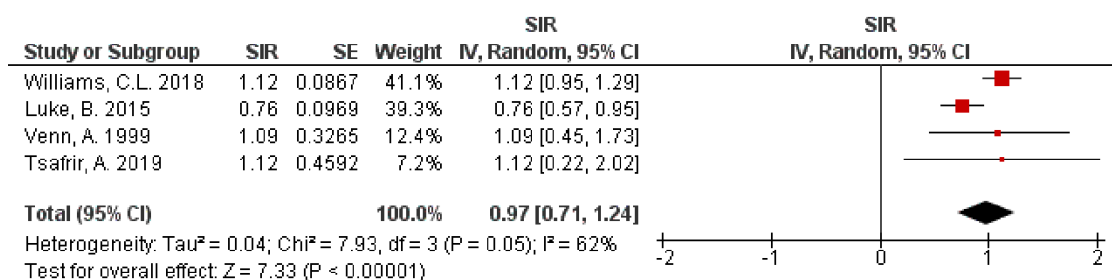


Fig. 3: Tree Diagram Comparative Analysis of the Standardized Incidence Rate (SIR) for Uterine Cancer in the IVF group in Studies 1999-2022

This analysis combined the results of four studies (Fig. 3), the standardized index of detection (SIR) of malignant neoplasms of the uterine body after IVF was used as the estimated indicator. Overall, the scores from the various individual studies were close to parity for the overall risk of malignant neoplasms of the uterine body.

According to the Cochran Q-test, the data are heterogeneous ($p < 1$), while the I^2 index shows a significant degree of heterogeneity ($I^2 = 62\%$). According to the data, a random effects model is used. The pooled analysis showed no statistically significant differences, SIR 0.97 [0.71, 1.24].

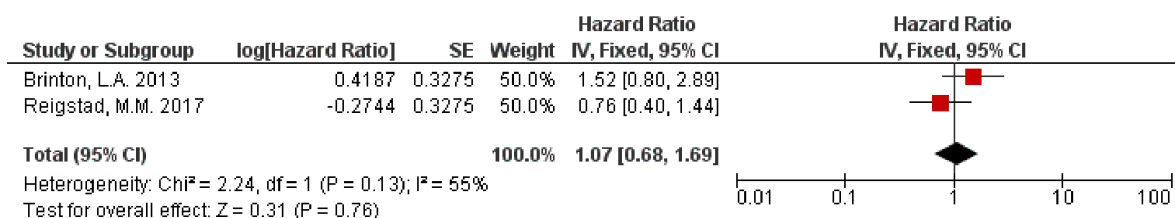


Figure 4: Tree Diagram Comparative Analysis of Hazard Ratio (HR) Indicators of Endometrial Cancer Development in the IVF Group in Studies 1999-2022

In total, according to the combined data of the two studies (Fig. 4), in accordance with the data of

the Cochran Q-test, the data are heterogeneous ($p > 1$), the I^2 indicator shows a significant degree

of heterogeneity ($I^2 = 55\%$). In this case, according to the accepted methodology, it is necessary to take into account, first of all, the data of the Chi-square test; accordingly, a model with a fixed effect is chosen. According to the results obtained, in general, there were no statistically significant differences in the hazard ratio (HR) of endometrial cancer development in the case of IVF - HR 2.15 [0.90, 5.17].

V. INTERPRETATION

Common fertility treatments may include the use of antiestrogen drugs to induce ovulation, such as clomiphene citrate or tamoxifen, either alone or as part of IVF cycles. Commonly used drugs also include human menopausal gonadotropins, recombinant follicle-stimulating hormone, and human chorionic gonadotropin. In a comparative cohort study involving 19,000 females, after a 17-year follow-up period, data were obtained in favor of the safety of the IVF method. The risk of developing endometrial cancer after ovarian stimulation according to IVF protocols was comparable with other methods that are used to treat infertility (SIR=1.41; 95% CI=0.77-2.37, $p>0.05$) [8]. Studies on the effect of these drugs on the incidence of endometrial cancer when used alone and as part of assisted reproductive technologies provide conflicting data, and study designs often do not allow us to speak with sufficient accuracy about the clinical structure of developing neoplastic processes, as well as about the representativeness of the data due to the small number and heterogeneity of the examined cohort of patients [8, 13, 25-30]. For example, some works found by the authors, unfortunately, do not structure the data obtained in accordance with the histological classification of uterine tumors, limiting themselves to division into neoplasms of the body and cervix. Limiting factors were also a small number of outcomes, short follow-up and early withdrawal of patients from the study.

Thus, the study of a possible relationship between the treatment of infertility in women and the development of malignant neoplasms of the endometrium is extremely relevant for further study, taking into account the shortcomings of studies that are available for evaluation today

[29]. Complicating the analysis of the situation is the fact that even infertility itself is associated with an increased risk of developing endometrial cancer (odds ratio, OR = 1.22; 95% CI: 1.13–1.33), as well as the absence of childbirth in history is a risk factor for the development of cancer of this localization (OR = 1.76; 95% CI: 1.59–1.94) [30].

Definitely, changes in hormonal status are considered as an important risk factor for EC. It is hormone-dependent type I endometrial carcinomas that are more common. [8,31]. In view of the similarity of the chemical properties of clomiphene citrate and tamoxifen, various authors actively discuss their pathogenetic relationship with endometrial cancer [26, 27]. However, opinions differ, and the data obtained do not allow us to speak unambiguously about the presence of an association.

Thus, several cohort studies have demonstrated an increase in the incidence of endometrial cancer among patients treated with clomiphene citrate [25, 12, 23, 32]. Moreover, it is discussed that the risk depends on the dose of the drug, the number of cycles of stimulation, the incidence of malignant neoplasms of the endometrium was significantly higher among women who used clomiphene citrate for six cycles or more [12].

It was also found that the risk of endometrial cancer was significantly higher in women treated with clomiphene citrate and human menopausal gonadotropin compared with the general population (SIR=5.0, 95% CI=2.15-9.85, $p<0.05$) [32]. In contrast, most studies have not confirmed these results and have not demonstrated a significant increase in the incidence of subsequent endometrial cancer in women treated in the past with clomiphene citrate, gonadotropins and IVF [31, 26,27]. In a retrospective study of 12,193 infertile women over a full 26 years of follow-up, there was no significant difference in risk of endometrial cancer with gonadotropins (RR = 1.34, 95% CI = 0.76). -2.37, $p>0.05$), clomiphene citrate (HR=1.39, 95% CI=0.96-2.01, $p>0.05$) or co-administration (HR=1.77, 95 % CI=0.98-3.19, $p>0.05$) compared with the control group [18]. In addition, according to a large cohort study of 29,700 women, the incidence of uterine cancer

was not higher than expected in women in the IVF group compared to the group of women who did not receive fertility treatment (SIR = 1.09, 95% CI = 0.45-2.61, $p > 0.05$) [21]. Due to the fact that the control group, which is women of the general population, may not be representative for comparison, it is legitimate to consider patients with infertility who do not plan pregnancy as controls [13, 27]. Interesting data is provided by a meta-analysis of five studies (776,224 women with infertility) that did not reveal an increased risk of developing endometrial carcinoma between groups of women, after treatment and without infertility treatment. In accordance with the data obtained, it is assumed that drug therapy for infertility can reduce the incidence of malignant neoplasms of the uterus from 2.22% to 0.14%. It was also found that the incidence of uterine neoplastic processes was statistically reduced in the group using IVF protocols (OR = 0.38; 95% CI = 0.30-0.47, $p < 0.05$) [33]. A meta-analysis combining 15 studies using the general population as a control group demonstrated a 1.8-fold increase in the risk of endometrial cancer in 1.7 million patients who underwent ovulation stimulation [27]. On the other hand, in the same systematic review, when the study group was compared with an untreated cohort of patients with infertility, there was no definite association between uterine malignancies and exposure to any drug [27].

Thus, the literature data make it possible to consider the ambiguous results of assessing the risk of developing endometrial cancer in patients in the IVF group. The structure of studies in the vast majority of cases does not allow accurately stratifying patients into subgroups depending on the therapy, dosage of drugs and the number of stimulation cycles and therefore determining the contribution of the pharmacological effects of drugs to the overall structure of the incidence of uterine cancer. There are a number of studies focused on assessing the direct impact of various pharmacological methods of infertility treatment on the risk of developing oncological processes in the organs of the female reproductive system, however, outside the context of in vitro fertilization methods, which is beyond the scope in Buryat republic. Fundamental and Clinical

of our study. Studies containing information on the available factors of infertility (male factor, female: pathology of the fallopian tubes, ovaries, endometriosis, etc.), for the most part, present these data as an introductory descriptive characteristic, which does not allow assessing the contribution of these factors to oncological risk.

VI. CONCLUSION

The data presented by various studies are heterogeneous and ambiguous. The structure of the conducted studies in some cases does not include detailed information about the study groups and does not allow us to speak accurately enough about the clinical structure of developing malignant neoplasms. The results of using various approaches to infertility treatment, protocols of assisted reproductive technologies described by the authors indicate the presence of certain risk factors in this category of patients, and the status of reduced fertility in itself is associated with an increased risk of developing malignant neoplasms of the uterus. Further research will allow clarifying and stratifying the risk of developing uterine cancer in the context of the complex structure of applied infertility treatment protocols, including in vitro fertilization, with an assessment of the specific contribution of each ovulation inducer individually or in combination with other methods that are used to overcome female infertility.

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Compliance with patient rights and principles of bio ethics. All patients gave written informed consent to participate in the study.

All authors made a significant contribution to the study and the article preparation, as well as read and approved the final version before its publication.

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Evaluating the Impact of Large Language Model AI on Acute Pancreatitis Management: A Chatgpt-based Investigation

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ABSTRACT

Background: Evidence-based management of acute pancreatitis (AP) is important for patient outcomes. The present study evaluated suggestions by artificial intelligence (AI) chatbot system, ChatGPT, for the management of acute pancreatitis, its alignment with clinical guidelines, and assistance in clinical decision-making.

Methods: Six questions on pancreatitis management were curated by experienced RACS-qualified general surgeons and were put forth to ChatGPT. The chatbot was also asked to provide five high-level evidence references to support each of its responses. Each response was analyzed for its accuracy and comprehensiveness with respect to current internationally recognized guidelines and by two Board-Certified General Surgeons for acute pancreatitis management, as well as for its spelling, grammar, and reference quality. A five-point Likert Scale was utilized to analyze ChatGPT's responses, with scores ranging from 1 (strongly disagree) to 5 (strongly agree). Ten questions were designed to assess accuracy, consistency, informativeness, reliability, and coherence.

Keywords: chatGPT, acute pancreatitis, management, artificial intelligence, large language model.

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Results: ChatGPT successfully adhered to clinical guidelines when generating recommendations for the management of acute pancreatitis. The depth of information remained general and non-specific but was presented in an academic manner with appropriate grammar, spelling and

sentence structure. ChatGPT missed pertinent references, with some being totally fabricated or erroneous.

Conclusion: ChatGPT holds promise for delivering prompt and accessible medical information to non-experts, which may benefit in situations where medical professionals and resources may be scarce or patients are reluctant to seek such services. The inclusion of aberrant or fabricated references is a challenge for researchers and clinicians and breaches academic integrity. Ethically, it is imperative for researchers to exercise prudence when utilizing ChatGPT for research purposes.

Keywords: chatGPT; acute pancreatitis; management; artificial intelligence; large language model.

I. INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease state of the pancreas, with well-established etiology, diagnostic criteria, and management guidelines. Gallstones and excessive chronic alcohol consumption are the most common causes, contributing to 75%-80% of all cases [1,2]. The Revised Atlanta Classification is an established diagnostic tool for pancreatitis with an emphasis on management dependent on the underlying cause and severity of the disease [3,4].

Chat Generative Pre-trained Transformer (ChatGPT) is a large language model (LLM) which has gained significant popularity in the field of medicine [5]. LLMs are advanced machine learning platforms designed to understand and

generate human-like text based on the models that are trained on [6]. Launched by OpenAI in November 2022, this software has numerous potential applications in clinical environments and research, and the LLM has already shown promise in producing accurate responses to clinical questions on topics like neuropathic pain, cirrhosis, knee and hip osteoarthritis, scaphoid fractures, and radiology reporting [5]. While multiple studies demonstrate its ability to generate high quality scholarly outputs, issues with consistency, specificity, and accuracy in its answers are faults documented commonly, and concerns of sources of information question its ethical use in medicine and research [7,8].

As AI continues to evolve at a rapid pace, its applications in clinical environments have garnered increasing interest. This research article endeavored to evaluate the performance of the ChatGPT-4 model to provide comprehensive, accurate, and coherent responses to inquiries pertaining to acute pancreatitis. The authors posit that the amalgamation of AI and natural language processing models, such as ChatGPT, within the fields of medicine and research holds substantial potential for propelling advancements in these disciplines but clinicians should tread with caution.

II. METHODS

The study assessed ChatGPT-4's ability to provide accurate, extensive and well synthesized answers that were congruent with current evidence-based literature and international guidelines. Furthermore, the quality of references it provided was evaluated. There were no exclusion criteria to ChatGPT's generated answers. No institutional ethics were required for analyzing the artificial chatbot and for this type of study's design (observational case study).

We presented ChatGPT-4 with six questions focused on acute pancreatitis, predominantly based on its cause, diagnosis, and management. The questions were developed and evaluated in conjunction with two Royal Australasian College of Surgeons (RACS) certified General Surgeons (AL and DD) with enormous experience in the

field. Questions aimed to determine the precision and depth of generated answers. Concurrently, three authors (DG, AS, and IS), conducted independent scoping literature searches using PubMed, EMBASE, Scopus, Cochrane CENTRAL and Google Scholar databases to identify high quality and impactful research publications relevant to each question. The outputs the AI provided were analyzed for accuracy against well-established evidence-based research and international guidelines primarily derived from our initial database search, and secondly by two RACS-certified General Surgeons (AL and DD). This combination of evidence-based research and the expert opinions of two general surgeons served as our comparator in analysing ChatGPT's responses. Throughout the questioning, ChatGPT was asked to provide five high level references to support its answer, which was assessed for quality, appropriateness, and existence, and again compared to our initial scoping database searches on the subject. References that were not found through the aforementioned databases and Google, were deemed to be non-existent references.

To enhance the robustness of our study and validate our observations more comprehensively, ChatGPT's responses were subjected to a detailed analysis using a five-point Likert Scale. This scale ranged from "strongly disagree" (1) to "strongly agree" (5), and was meticulously designed to assess various dimensions of ChatGPT's output, including accuracy, consistency, informativeness, reliability, and coherence. To ensure a wide-ranging evaluation, ten meticulously crafted questions targeting these specific aspects were formulated. These questions were independently reviewed and scored by a diverse panel comprising three junior doctors (DG, AS, and IS) and two experienced General Surgeons (AL and DD). This composition of evaluators was strategically chosen to incorporate perspectives ranging from early-career medical professionals to seasoned experts, thereby enriching the assessment with varied levels of clinical expertise and experience. In addition to the Likert Scale evaluation, a qualitative component was integrated into the methodology. Panel members

were encouraged to provide narrative feedback and annotations on each of ChatGPT's responses, aiming to capture nuanced insights beyond the quantitative scores. This qualitative feedback focused on identifying specific strengths and weaknesses in the AI's responses, offering a more granular view of its performance in mimicking clinical reasoning and adhering to medical guidelines. In instances where discrepancies in scoring arose among the panel members, these were not merely noted but actively discussed in structured consensus meetings. These discussions aimed to explore the underlying reasons for differing opinions, fostering a deeper understanding of the evaluation criteria and potentially revealing any biases or interpretational variations.

IV. RESULTS

The first question posed was "In 200 words, what are the causes of acute pancreatitis? Provide 5 high level evidence references" (Figure 1). Overall ChatGPT-4 provided an extensive, factual and coherent answer which correctly identified gallstones and chronic alcohol use to be the two leading causes of acute pancreatitis with incidences similar to current literature [4,9]. Whilst large incidence ranges were given, it is well-known that incidence rates differ quite significantly between geographic regions and socioeconomic strata [10]. The brief pathophysiological description of gallstone pancreatitis was accurate, outlining that the obstructive pathology increases upstream pancreatic duct pressure [3]. In contrast, the pathophysiological description of alcohol-induced pancreatitis did not disclose the lack of a definitively known mechanism that exists and explored just one of several proposed mechanisms of how alcohol contributes to acute pancreatitis. Other common causes of AP were explored including hypertriglyceridemia, medication toxicity and infectious agents, with appropriate examples being given for the latter two [3,10]. A breadth of less common causes was correctly listed, providing a holistic answer within the proposed word limit. In saying this, idiopathic pancreatitis was not listed which makes up a

significant proportion of affected patients, as only 75-85% of etiologies are easily identified [9]. The answer was well synthesized and formatted making for easy viewing. All 5 references provided were high quality and relevant to the causes identified.



In 200 words, what are the causes of acute pancreatitis? Provide 5 high level evidence references.



Acute pancreatitis is an inflammatory condition of the pancreas characterized by abdominal pain and elevated pancreatic enzymes. The causes of acute pancreatitis can be divided into various categories:

1. Gallstones: Obstruction of the pancreatic duct by gallstones is one of the most common causes of acute pancreatitis, accounting for 30-60% of cases. Gallstones can lead to increased pressure in the pancreatic duct, causing inflammation and injury to the pancreas.

Reference: Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013 Sep;108(9):1400-15.

2. Alcohol: Alcohol-induced pancreatitis is another major cause, responsible for 25-35% of cases. Chronic heavy alcohol consumption can cause direct toxic injury to pancreatic cells and increase the risk of pancreatitis.

Reference: Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet. 2015 Jul 4;386(9988):85-96.

3. Hypertriglyceridemia: High levels of triglycerides in the blood can lead to acute pancreatitis, typically when levels exceed 1000 mg/dL.

Reference: Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol. 2014 Mar;48(3):195-203.

4. Medications: Certain medications, such as diuretics, immunosuppressants, and some antiretroviral drugs, can induce pancreatitis as a side effect.

Reference: Nitsche CJ, Jamieson N, Lerch MM, Mayerle JV. Drug induced pancreatitis. Best Pract Res Clin Gastroenterol. 2010 Oct;24(5):143-55.

5. Infections: Viral infections (e.g., mumps, coxsackievirus), bacterial infections (e.g., Legionella, Mycoplasma), and parasitic infections (e.g., Ascaris lumbricoides) can cause acute pancreatitis.

Reference: Parenti DM, Steinberg W, Kang P. Infectious causes of acute pancreatitis. Pancreas. 1996 Nov;13(4):356-71.

Other less common causes include autoimmune conditions, trauma, metabolic disorders, and genetic factors. It is essential to identify and manage the underlying cause to effectively treat acute pancreatitis.

Figure 1: Prompt 'in 200 Words, What are the Causes of Acute Pancreatitis? Provide 5 High Level Evidence References'

The second question asked to the chatbot was "In 200 words, what is the diagnostic criteria for acute pancreatitis? Provide 5 high level evidence references" (Figure 2). The diagnostic criterion for acute pancreatitis is well-established and acknowledged internationally. ChatGPT was able

to correctly identify the Revised Atlanta Classification model and gave an in-depth explanation of what it entails to reach a diagnosis. Whilst accurate, there was no expansion of the answer to diagnose specific etiologies through investigations such as biliary tree imaging or lipid

profile laboratory investigations, which are important aspects of diagnosis that dictate specific and definitive management principles [10]. Of the 5 references supplementing its answer, 4 were existent publications appropriate to the topic in question, however the final was a fabricated resource (Figure 2, reference #5, Van Geenen et al).

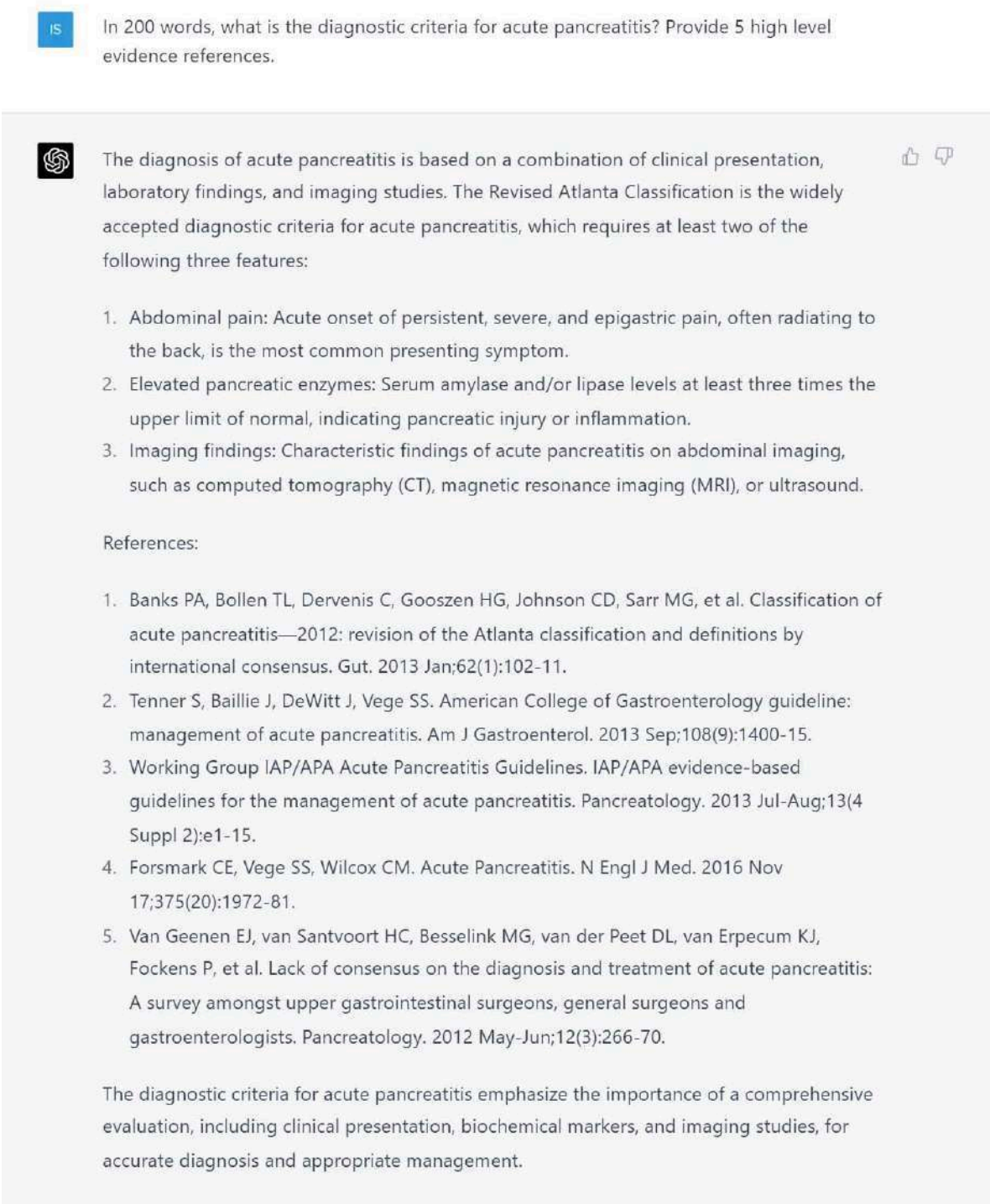


Figure 2: Prompt ‘in 200 words, what is the Diagnostic Criteria for Acute Pancreatitis? Provide 5 High Level Evidence References’

The following question was “In 300 words, how is acute pancreatitis managed? Provide 5 high level evidence references” (Figure 3). Given the array of management strategies that can be employed based on disease severity and particular etiology, we encouraged a more comprehensive answer.

based on disease severity and particular etiology, we encouraged a more comprehensive answer. Once again, a detailed answer was provided with factual information primarily outlining the supportive care routinely applicable. This included fluid resuscitation, pain management and nutritional support which is the mainstay treatment for all cases, and often for those with mild disease [4,10]. Notably, early enteral feeding was mentioned but not stated as the standard of care which is not consistent with current guidelines [11]. The use of antibiotics was qualified in ChatGPT's response, as they are only indicated in infected pancreatic necrosis or extra pancreatic infections [12]. Intensive care involvement was correctly identified as an avenue in severe cases especially with organ failure [13].

Disappointingly, management directed at specific etiologies and complications were poorly answered, being vague and superficial. This aspect of the answer alluded to "endoscopic, radiological and surgical interventions," but no examples such as ERCP, percutaneous drainage, cholecystectomy nor their indications were given. Although five high-quality references were provided, some proved to be irrelevant or contradictory. For instance, one reference by Mounzer et al [31] was associated with the pain management point but ChatGPT lacked evidence directly related to pain management strategies. Another reference by Bakker et al [32] contradicted the nutritional support recommendation offered by ChatGPT, thereby undermining the reliability of the cited references.

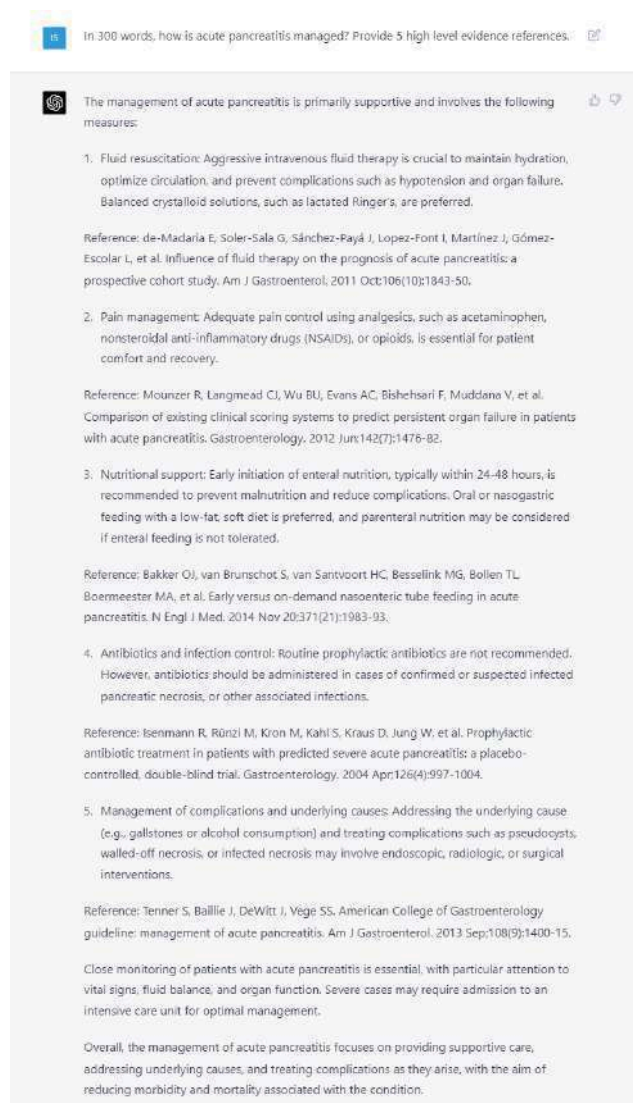


Figure 3: Prompt 'in 300 words: How is Acute Pancreatitis Managed? Provide 5 High Level Evidence References

The next question extended on the previous, asking more specifically “In 200 words, what’s the management for necrotizing pancreatitis? Provide 5 high level evidence references” (Figure 4).

ChatGPT displayed its answer in a similar format to the previous and in doing so was largely repetitive in the information it provided. It failed to clearly discriminate between sterile versus infected pancreatitis, which have different management approaches as well as complication and mortality rates (5-10% versus 20-30%, respectively) [10,14]. Fluid resuscitation, nutritional support and intensive care strategies once again were cornerstones in their answers; however, pain management was excluded.

Prophylactic antibiotic therapy and radiological/endoscopic/surgical drainage was correctly established for infected necrotizing pancreatitis management [14]. However, this was not accompanied by specific management principles of sterile pancreatitis, which generally consists of supportive treatment and delayed necrosectomy in symptomatic cases. Its last point was additionally futile given acute pancreatitis, regardless of necrosis, is often managed with multidisciplinary collaboration between general surgeons, gastroenterologists, intensivists, pathologists, radiologists and dieticians [15]. As such, this doesn’t necessarily represent a key management principle of necrotizing pancreatitis. Two of the five references were shared with the previous question. One reference was fabricated (Figure 4, reference #1, Mayerle et al), whilst the remaining four were high quality publications related to the question.



In 200 words, what's the management for necrotising pancreatitis? Provide 5 high level evidence references.



The management of necrotizing pancreatitis focuses on supportive care, infection control, and intervention for complications when necessary. Key aspects include:



1. Fluid resuscitation and organ support: Aggressive intravenous fluid therapy is crucial, and organ support, such as mechanical ventilation or renal replacement therapy, may be required in severe cases.

Reference: Mayerle J, Dummer A, Sendler M, Malla SR, van den Brandt C, Teller S, et al. Intra-abdominal pressure during fluid resuscitation is a sensitive end point for fluid management in acute pancreatitis. *Ann Surg*. 2020 May;271(5):942-51.

2. Nutritional support: Enteral nutrition, preferably via a nasogastric or nasoenteric route, should be initiated early to prevent malnutrition and reduce complications.

Reference: Bakker OJ, van Brunschot S, van Santvoort HC, Besselink MG, Bollen TL, Boermeester MA, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med*. 2014 Nov 20;371(21):1983-93.

3. Antibiotics and infection control: Prophylactic antibiotics are not routinely recommended; however, they should be administered if infected pancreatic necrosis or other associated infections are suspected or confirmed.

Reference: Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung W, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology*. 2004 Apr;126(4):997-1004.

4. Minimally invasive intervention: In cases of infected pancreatic necrosis, a step-up approach, including percutaneous or endoscopic drainage followed by minimally invasive necrosectomy if needed, is preferred over open necrosectomy.

Reference: van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010 Apr 22;362(16):1491-502.

5. Multidisciplinary management: Close collaboration with a multidisciplinary team, including gastroenterologists, surgeons, interventional radiologists, and critical care specialists, is essential for optimal patient outcomes.


Reference: Vege SS, DiMagno MJ, Forsmark CE, Martel M, Barkun AN. Initial medical treatment of acute pancreatitis: American Gastroenterological Association Institute technical review. *Gastroenterology*. 2018 Apr;154(4):1103-39.


Figure 4: Prompt ‘in 200 words, What’s the Management for Necrotizing Pancreatitis? Provide 5 High Level Evidence References’

The fifth question was designed with more what is the optimal timing of laparoscopic surgical focus, asking ChatGPT, “In 200 words, cholecystectomy for gallstone pancreatitis?”

Provide 5 high level evidence references" (Figure 5). ChatGPT correctly identified the decision around surgery timing depends on the severity of pancreatitis. While a complex decision, ChatGPT correctly indicated early laparoscopic cholecystectomy (ELC) in mild disease, versus delayed laparoscopic cholecystectomy (DLC) in moderate to severe disease and provided timelines for management. Although no consensus exists on the definition of "early," ELC within 72 hours as

recommended by ChatGPT, is evidenced by numerous studies such as the PONCHO trial [16]. ChatGPT also synthesized the underlying reasons behind these guidelines, including reducing recurrence, complication, morbidity and mortality rates [17]. Five true and high-quality publications were referenced, including a key systematic review by van Baal et al, and a publication on the PONCHO trial by da Costa et al.

 In 200 words, what is the optimal timing of laparoscopic cholecystectomy for gallstone pancreatitis? Provide 5 high level evidence references.



The optimal timing of laparoscopic cholecystectomy for gallstone pancreatitis depends on the severity of the pancreatitis. Current evidence suggests the following:

1. Mild gallstone pancreatitis: Early laparoscopic cholecystectomy, preferably within 72 hours of symptom onset or during the index hospitalization, is recommended to reduce the risk of recurrent pancreatitis and other gallstone-related complications.

Reference: Aboulian A, Chan T, Yaghoubian A, Kaji AH, Putnam B, Neville A, et al. Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: a randomized prospective study. *Ann Surg.* 2010 Apr;251(4):615-9.
2. Moderate to severe gallstone pancreatitis: In more severe cases, cholecystectomy is typically delayed until clinical and laboratory parameters have improved, and local complications, such as pancreatic necrosis, have stabilized. This often occurs within 2 to 4 weeks of symptom onset.

Reference: van Baal MC, Besselink MG, Bakker OJ, van Santvoort HC, Schaapherder AF, Nieuwenhuijs VB, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. *Ann Surg.* 2012 May;255(5):860-6.

Early cholecystectomy in mild cases and a more conservative approach in moderate to severe cases have been shown to reduce morbidity, mortality, and the risk of recurrent pancreatitis.

Reference: Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol.* 2013 Sep;108(9):1400-15.

Reference: Ito K, Ito H, Whang EE. Timing of cholecystectomy for biliary pancreatitis: do the data support current guidelines? *J Gastrointest Surg.* 2008 Oct;12(12):2164-70.

Reference: Da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet.* 2015 Oct 17;386(10000):1261-8.

Figure 5: Prompt ‘in 200 words, what is the Optimal timing of Laparoscopic Cholecystectomy for Gallstone Pancreatitis? Provide 5 high Level Evidence References’

The final question requested was “In 200 words, provide future directions of research for the management of acute pancreatitis? Provide 5 high level evidence references” (Figure 6). ChatGPT accurately identified the significance of biomarkers related to inflammatory pathophysiology and targeted therapies [18] but responses were not new ideas or very timely. While nutritional support was discussed, the cited reference was outdated [44], and more recent

findings on parenteral nutrition and immuno-enhanced nutrients or probiotics were omitted [19]. The suggestion to investigate genetics in acute pancreatitis was pertinent, but the accompanying reference was not only outdated, but also more tailored to chronic pancreatitis [43]. Overall, ChatGPT's response was adequate, touching on several key research areas, but only three of five references were high-quality and relevant.

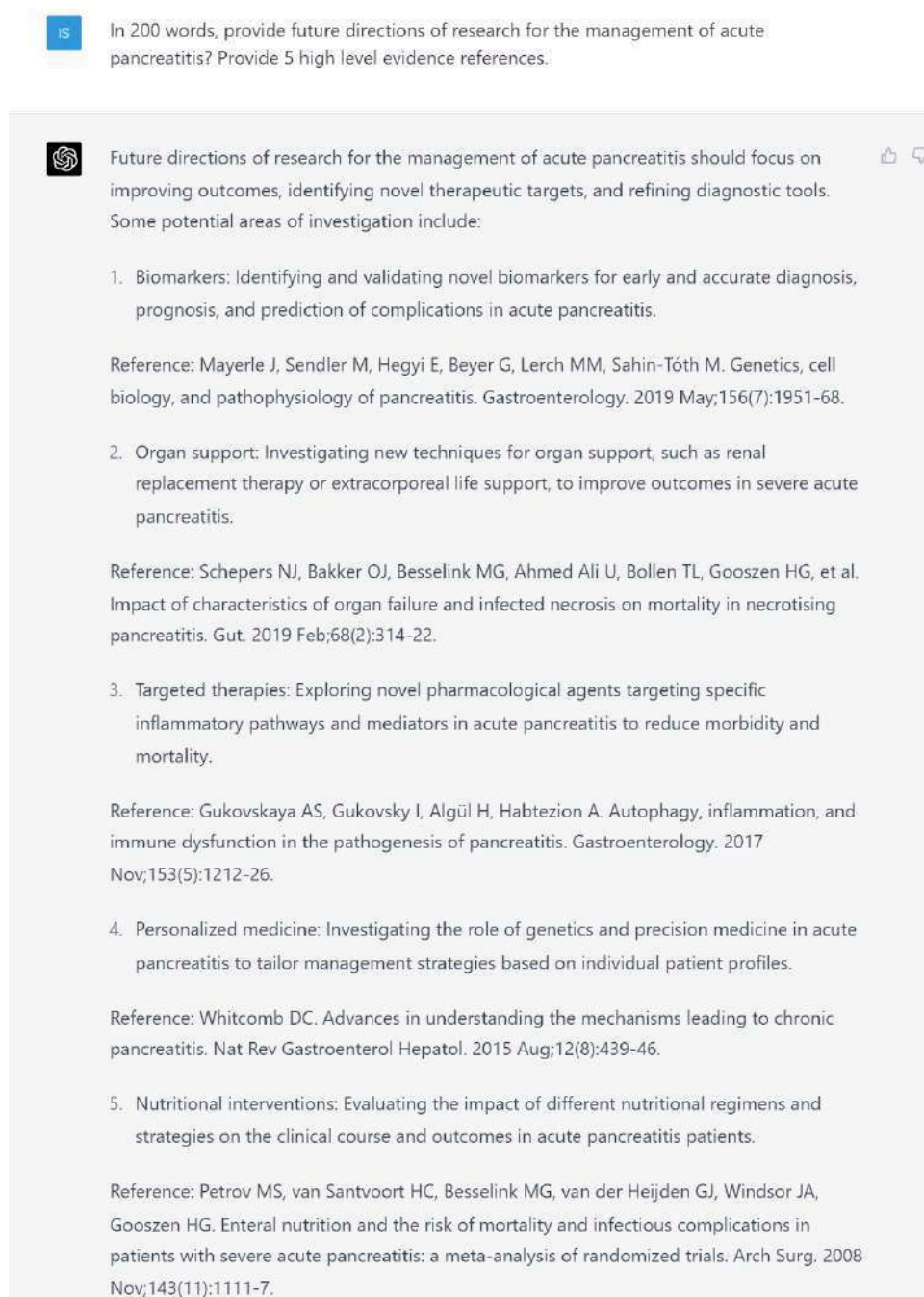


Figure 6: Prompt ‘in 200 words, Provide Future Directions of Research for the Management of Acute Pancreatitis? Provide 5 High Level Evidence References

In performing a subjective qualitative assessment of ChatGPT's abilities using a Likert Scale (Table 1) we were able to unify its attributes and summarize the overall performance of ChatGPT in this study. Our findings demonstrated scattered scores for desirable characteristics of the Chatbot. ChatGPT's ability to comprehend complex questions and provide accurate answers received scores of 4, and its ability to synthesize its

answers coherently and utilise academic terminology received scores of 5. We were indifferent to its ability to provide in-depth and wholistic information, hence these attributes were given scores of 3. Concerningly, questions directed to its referencing abilities received scores of 2. A high score of 5 was given for its general medical knowledge and 4 for its specific medical knowledge.

Table 1: Evaluation of ChatGPT's Responses using a Likert Scale

| | Strongly Disagree-1 | Disagree-2 | Neither Agree or Disagree | Agree -4 | Strongly Agree - 5 |
|--|---------------------|------------|---------------------------|----------|--------------------|
| ChatGPT provides accurate answers consistently when answering questions | | | | X | |
| Chat CPT can Comprehend complex questions and provide appropriately directed answers accordingly | | | | X | |
| ChatCPT Provides in-depth information when answering questions | | | X | | |
| ChatGPT provides a wholistic breadth information when answering question | | | X | | |
| ChatGPT provides true citations consistently when prompted | | X | | | |
| ChatGPT provides high quality citations consistently when prompted | | X | | | |
| ChatCPT produces coherent and well synthesized answers | | | | | X |
| ChatCPT uses academic medical terminology appropriately when answering questions | | | | | X |
| ChatCPT is a valuable source of general medical knowledge | | | | | X |
| ChatCPT is a valuable source of specific medical knowledge | | | | X | |

V. DISCUSSION

ChatGPT consistently performed excellently when generating responses to questions on the management of acute pancreatitis. As other studies have noted, the chatbot has the potential to assist within clinical environments as an adjunctive management tool, or for patients to utilize at home for their self-education. Further to its application here, there is convincing potential to adopt its use more confidently and safely in information gathering for both patients and clinicians, as well as in the research domain. Specifically, the chatbot consistently constructed accurate, easily understandable sound answers, with minimal pitfalls, which would rival the communication of many doctor-patient conversations where medical jargon is a barrier to

patient understanding. In addition, ChatGPT often derived its answers from high quality medical publications on request, which may enhance doctor confidence when utilising AI. Currently, the use of LLMs may improve patient outcomes in remote and rural regions or emergencies where prompt diagnosis and management in the context of resource scarcity would optimize patient safety.

We hypothesize that multiple factors contribute to the quality disparity between this study and prior ChatGPT research. Our study used the latest ChatGPT version with enhancements by OpenAI, potentially improving learning, data collection, and answer quality. Perhaps, with acute pancreatitis having well-studied and established guidelines in general surgery, the likelihood of

ChatGPT providing aberrant information is minimized, compared with more nuanced and evolving topics. The relative consistency in the literature for pancreatitis would presumably allow for greater accuracy, consistency in responses and basis for choosing references. Despite this, investigations into ChatGPT-4 for more poorly understood pathologies are yet to be undertaken, and similar improvements could be observed in the advent of the new version.

Although the upsides are clear, ChatGPT has previously shown inadequate consistency and accuracy in information gathering depicted across an array of topics that preclude its use in clinical medicine. A recent systematic review explored ChatGPT's strengths and limitations for its use in healthcare education, research, and practice, finding numerous strengths which were also accompanied by concerns in 58/60 (96.7%) of its analysed records. This encompassed ethical, copyright, legal, risk of bias, plagiarism, inaccuracy with risk of hallucination, limited knowledge and incorrect citation concerns [20]. Herein, the generation of irrelevant and non-existent citations was infrequent but none-the-less present in this study, as has been problematic previously [21]. So far, ChatGPT has been restricted to certain areas of medicine and this is the first to investigate its use with acute pancreatitis being the clinical presentation.

Despite promising results in our study, it would be negligent not to identify the pitfalls of ChatGPT which could lead to disastrous consequences in clinical practice, research and education. For example, the occasional provision of outdated, inaccurate, or superficial information highlights the need for further model refinement and updated medical literature training before such a tool is confidently used for information gathering and synthesis. Specifically, the generation of fabricated or irrelevant references, despite infrequent, raises great concern and can be fatal in the real clinical setting. This proves to be a drastic issue yet to be resolved by the developers, which questions the reliability, consistency and evidence base of answers produced by the Chatbot. In the field of medicine, where clinical decisions are derived from foundational evidence,

this is very problematic, and a major contributor to inaccurate information and knowledge gaps that ChatGPT may produce. To maintain scientific integrity, a necessary improvement of ChatGPT lies in enhancing its citation detection capabilities through vigorous cross checking with reputable peer-reviewed databases such as what we have done through our methodology. Particularly, artificial intelligence systems need to be created to avoid the common "plausible combination" type references whereby a combination of vaguely relevant sources will be summated to produce a false reference. This remains the most worrying aspect of ChatGPT, with additional academic integrity, plagiarism and ethical concerns stemming from this consistent downfall. It should also be noted that ChatGPT can only gather data prior to September 2021, and thereby may miss emerging research or guidelines. ChatGPT's current knowledge limitations and inability to consider individual patient factors also flies in the face of modern medicine's best attempt at attending to each patient as individuals, and the multidisciplinary team who take center stage in many walks of medicine. How ChatGPT will fit into these paradigms of clinical practice will be interesting in the coming years. If these concerns can be addressed, the application of large language models in clinical practice could drive transformative changes in healthcare.

For its use in clinical medicine, ChatGPT needs to be able to reliably deliver sound information based on high quality evidence-based literature. Currently, concerns surrounding its data collection and reliability of answers raise hesitation to the medical community to confidently adopt it into their practice. As a result, it is of vital importance that all users, especially medical practitioners, exercise caution when using these LLMs and understand their limitations.

Lateral to ChatGPT's potential in clinical practice, is its use in medical education. The promising but not completely refined results that this study and others have shown, opens the door for using ChatGPT as a tool to educate medical students and doctors especially on well-established and well understood common pathologies. Harnessing

this as a modern education technology can help overview, summarise and consolidate key clinical learning points for different pathologies as well as the basic scientific understanding behind clinical practices. Once again, limitations would be shared with its use in clinical practice, and therefore not only should be used cautiously, but may have the potential to be abused through plagiarism.

Our study had multiple limitations that should be acknowledged to guide future research in this field. Firstly, our study design did not analyse any temporal data in the form of re-asking the same question to the Chatbot at a different point in time to compare generated answers over time. This would be valuable as the Chatbot continues to develop. Additionally, word limits were generally kept to 200 words which may restrict the quality and depth of answer provided by ChatGPT. This decision was made to encourage a response that was precise with enough room to briefly expand on its answer, which we believe is reflective of how doctors would primarily utilise Chatbots.

Finally, questions were generally open-ended which may impact the Chatbot's interpretation and therefore answer. These limitations encourage the need for further evaluation of LLMs as they continue to improve prior to integration to healthcare. Thus, future research should encompass the evaluation of specific and targeted questions and do so at different time points as the technology develops. Strategies like cross-verification with current medical databases to mitigate poor quality referencing would be insightful to ensure AI's safe integration into clinical decision-making. We focused on evaluating AI responses qualitatively against clinical guidelines, which begs the need for complimentary quantitative analysis.

VI. CONCLUSION

ChatGPT had excellent responses to clinical questions regarding acute pancreatitis management. While ChatGPT shows promise in supporting clinical decision-making, it is essential to ensure its responsible integration into clinical practice through continuous refinement, up-to-date training, and collaboration with

healthcare professionals. Future research should continue to evaluate different aspects of LLMs potential and applications in medicine as they continue to be refined and perform statistical analysis of their utility and limitations. Furthermore, wholistic future research should focus on evaluating the long-term effects of AI chatbots on patient outcomes, satisfaction, and healthcare resource utilization in various clinical settings.

Statements and Declarations:

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None

Conflict of Interest

The authors declare no Conflict of Interest for this article.

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Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

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