Yiming Gao, MD[1,*] and Samantha L. Heller, PhD, MD[1]

[1]New York University–Langone, Department of Radiology, New York, NY, USA

*Address correspondence to Y.G. (e-mail: Yiming.Gao@nyulangone.org)

Abstract

Breast cancer screening has been highly successful in women in reducing mortality through early detection. In comparison, clinical detection of breast cancer remains the norm in men, and delay in diagnosis is reflected by a persistent survival disparity compared to women despite advances in modern therapy. Male breast cancer presents an interesting dilemma. While mammography is highly sensitive and specific for male breast cancer, routine screening is not justified by the overall low disease incidence. Yet there has been interest in leveraging mammography in targeted screening of men with identifiable risk factors to allow early detection, and early data may support this approach. The purpose of this article is to explore the potential utility of targeted breast cancer screening in men by examining unique clinical and biologic characteristics of male breast cancers that may lend themselves to mammographic detection. We will also discuss available evidence in screening outcomes in men and summarize recent updates in risk management recommendations in Society guidelines.

Key words: male breast cancer; breast cancer in men; targeted screening; high risk screening; mammography screening; mammography in men.

Introduction

Breast cancer screening is not routinely performed in men because of a low disease incidence (1). Compared to women, who have a 1 in 8 lifetime risk of breast cancer, the risk in men is approximately 1 in 800 (2). Yet breast cancer is a clinically significant disease in men, as late presentation often results in advanced-stage disease and worse outcomes (3). In the United States in 2022, an estimated 2710 new cases of invasive breast cancer will occur in men, and 530 are expected to die from it (2). The age-adjusted incidence of male breast cancer has risen steadily from 0.85 per 100 000 in 1975 to 1.28 per 100 000 in 2020, and the rate of increase in incidence of breast cancer in men is higher than in women based on Surveillance, Epidemiology, and End Results Program data (4). Despite advances in modern therapy, a survival disparity persists between men and women. Registry data from the National Cancer Database between 2004 and 2014 comparing 16 025 male and 1 800 708 female patients with breast cancer showed a higher breast cancer mortality in men across all disease stages, with a 19% higher fully adjusted overall mortality in men compared to women (3). Yet there is uncertainty as to how to bridge the gap to improve breast cancer outcomes in men because of a paucity of data.

The purpose of this article is to explore the potential utility of targeted breast cancer screening in men, by examining unique clinical and biologic characteristics of male breast cancers that may lend themselves to mammographic detection. We will also discuss available evidence in screening outcomes in men and summarize recent updates in risk management recommendations in Society guidelines.

Natural History

Male breast cancer is predominantly ductal in origin (90%) because of a lack of lobular elements in the male breast (5). In a large pathology review with genetic sequencing of 1328 invasive breast cancers in men, ductal carcinoma in situ (DCIS) represented the most common precursor lesion (98%) demonstrated by genomic concordance with the adjacent invasive

Key Messages

- Breast cancer incidence in men continues to rise over time, and survival disparity between men and women persists despite modern therapy.
- Mammography is highly sensitive and specific for male breast cancer, but it is currently largely reserved for diagnostic evaluation of symptomatic men.
- Targeted mammography screening in men at elevated risk for breast cancer may be of benefit, and it has been shown to depict preclinical cancers with a cancer yield on par with that in average-risk women, suggesting potential to improve clinical outcomes.

disease (6). Mammographic imaging earlier in the course of carcinogenesis, therefore, likely provides an opportunity for early detection, as DCIS typically manifests as calcifications. Indeed, in population-based breast cancer screening in women, DCIS now comprises up to 25% of all screen-detected cancers, which speaks to the high mammographic sensitivity for calcified DCIS lesions (7). Currently, it is uncommon to encounter calcifications without an associated mass in men presenting with symptomatic breast cancer in the diagnostic setting (8,9). However, data comparing screening and diagnostic outcomes in men have shown a significantly higher likelihood of detecting DCIS calcifications alone on mammography in the screening group compared to the diagnostic group (60% vs 0%) (9). Therefore, in situ breast cancers in men may be well delineated on mammography.

The biologic profile of male breast cancer appears to resemble that of the more indolent variety of late-onset breast cancer in postmenopausal women (10). Male breast cancers are overwhelmingly luminal type cancers and hormone receptor positive (>90%), with basal-like and triple receptor negative cancers being exceedingly rare (<0.5%) (5). Papillary carcinoma is the second most common breast cancer type in men and may present as round or oval slow-growing masses. Thus, invasive breast cancers are typically well depicted on mammography and would be unlikely to escape detection as interval cancers in routine screening. In fact, two retrospective studies of men at elevated risk for breast cancer who underwent annual mammography screening both showed no interval cancers (9,11). Yet, despite the less aggressive molecular profile of male breast cancer, men with breast malignancy typically present with larger tumor size (>2 cm), greater likelihood of lymph node involvement (60%), more advanced disease stage (40% stage III/IV), and poorer overall survival compared to women (3,9,12–14). This survival disparity between men and women is evident stage for stage and most pronounced in early disease. Among patients with stage I or II breast cancer, men have significantly worse survival than women (median survival, 6.1 vs 14.6 years), underscoring a need for early detection (15). Early disease in men may also be more consequential due to anatomy: a smaller breast volume may predispose to a greater propensity for lymphovascular spread via tumor proximity to the dermal and subcutaneous lymphatic networks (16–18).

Clinical Detection

Clinical detection of breast cancer in men is confounded by a preponderance of benign findings. While the clinical breast exam has a high negative predictive value (NPV) in men (99.8%–99%), sensitivity is limited and variable depending on clinical experience (42.7%–88.2%) (19,20). In comparison, diagnostic mammography in symptomatic men has a sensitivity of 94.7%–100% and NPV of 99%–100% (20–22). Gynecomastia is by far the most common cause of breast symptoms in men, accounting for 62%–78% of all diagnoses in men who undergo breast imaging (22,23). When clinical exam findings are consistent with gynecomastia, imaging is usually not indicated (24). Yet, because gynecomastia frequently presents with unilateral symptoms, and because gynecomastia coexists with male breast cancer in approximately 50% of cases, imaging evaluation is often pursued to increase diagnostic confidence (21). In theory, clinical distinction between gynecomastia and breast cancer should be possible in most cases. Gynecomastia occurs centrally in the retroareolar region and typically presents as a tender palpable lump, whereas breast cancer is often eccentric and not usually associated with pain (20). However, location alone is not a reliable indicator of benignity, as up to 52% of male breast cancers are indeed centrally located (25). Presence of additional associated symptoms such as skin or nipple retraction and nipple discharge are highly suspicious for malignancy (positive predictive value, 25%–57%), particularly when accompanied with axillary adenopathy, and should be thoroughly evaluated (26,27).

Breast Imaging

The role of breast imaging in the evaluation of symptomatic men is relatively well established (24) (Table 1). Diagnostic mammography is the mainstay of male breast imaging, and it is highly sensitive (94.7%–100%) and specific (90%–96%) for cancer, with a near 100% NPV (99%–100%) (20–22). Mammography is highly accurate in distinguishing between benign and malignant findings in the male breast, and it outperforms clinical exams in establishing benign diagnoses to provide answers and reassurances (28,29). Mammography alone is diagnostic for gynecomastia in 90% of cases (dendritic and nodular subvariants) and has a characteristic depiction of fan-shaped or flame-shaped subareolar radiodensity that is pathognomonic (28) (Figure 1). When gynecomastia is the sole finding on mammography, US is usually not indicated due to a potential for false positives (1.8%) (30). However, if clinical and mammographic findings are suspicious for cancer, US is highly specific and allows for targeted breast and axillary evaluation (20). In cases in which mammography findings are indeterminate or may be obscured

Table 1. The American College of Radiology Appropriateness Criteria for Evaluation of the Symptomatic Male Breast (2018) (24)

Age	Presentation	Appropriate Initial Imaging
Any age	Clinical exam consistent with gynecomastia	None
<25 years	Indeterminate palpable breast mass	US +/- Mammogram/DBT
≥25 years	Indeterminate palpable breast mass	Mammogram/DBT +/- US
Any age	Clinical exam suspicious for cancer Palpable mass, nipple retraction, nipple discharge, or axillary lymphadenopathy	Mammogram/DBT/US

Abbreviation: DBT, digital breast tomosynthesis.

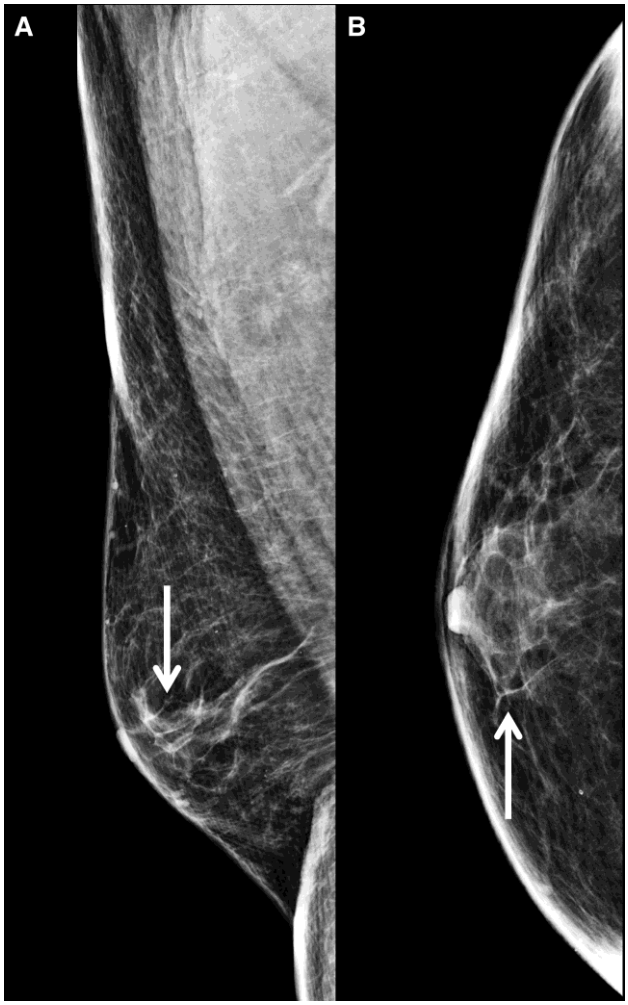

Figure 1. Images of a 76-year-old man who underwent mammography screening status post left mastectomy for prior breast cancer. Right mammogram in mediolateral oblique (**A**) and craniocaudal (**B**) views demonstrates flame-shaped subareolar radiodensity consistent with gynecomastia (arrows). No suspicious findings were identified in the right breast.

by tissue (eg, diffuse gynecomastia), US can be performed to increase sensitivity for cancer (31).

Diagnostic mammography is currently reserved for men 25 years or older who present with breast symptoms, as male breast cancer is rarely seen before age 40 (19,24). Indeed, despite superb performance of mammography, breast cancer yield is relatively low even in the diagnostic setting, which is primarily a function of low disease incidence in a population overrepresented by younger individuals with benign breast symptoms. Yet there is value in providing assurances in symptomatic men. While breast imaging is an important adjunct to clinical assessment in men, it is currently mainly used to exclude the possibility of cancer and to characterize cancer when presented clinically. Leveraging the high sensitivity of mammography to allow early detection of breast cancer in men via screening is a relatively newer and more controversial area of interest. While breast cancer screening is not currently widely adopted because of a paucity of data, consideration is worthwhile in the interest of improving patient outcomes.

The Goal of Screening

According to the National Cancer Institute, the goal of screening is to identify cancer early (before symptoms) so that it may be successfully treated to reduce mortality (32).

Decision to screen is predicated by well-established World Health Organization criteria that must be met (33). First, the disease should pose an important health problem. Second, the disease must have a detectable preclinical phase. Third, treatment of this disease before onset of symptoms offers benefits compared with treatment after symptom onset. Fourth, the screening test must have acceptable levels of accuracy and cost. Finally, accepted treatment exists for recognized disease and facilities for diagnosis and treatment are widely available (33–35).

Mammography screening has been highly successful in women in reducing breast cancer mortality via early detection, but its role in men is less well understood. Despite being uncommon, male breast cancer has a rising incidence worldwide and poses an important health problem for individual patients (36). The disease burden of breast cancer in men is currently disproportionate, with symptomatic presentation being the norm and 40% presenting as late-stage disease; a stark contrast with female breast cancer detection, for which now 25% of all newly diagnosed cancers

are in situ disease due to screening (7). Since male breast cancer is predominantly ductal and preceded by DCIS, it has a detectable preclinical phase for which mammography is highly sensitive (Figure 2). Breast cancer treatment at an early stage portends better prognosis in men just as in women. Male breast cancer survival by stage with modern therapy (2007–2016) based on data from the Centers for Disease Control National Program of Cancer Registries demonstrates markedly improved 5-year survival in localized stage disease than in distant stage disease (98.7% vs 25.9%) (37). Mammography is highly sensitive and specific for male breast cancer; however, there is currently no data on cost-effectiveness of screening in men. Finally, breast cancer imaging and treatment are widely available and the framework for screening and therapy already exists for women.

So the primary challenge in effectively screening for male breast cancer is likely one of scale. Targeted risk-based screening in men at elevated risk for breast cancer can be and has been shown to be of benefit in retrospective series, suggesting a potential to improve clinical outcomes (9,11).

Risk Assessment

Risk-based screening requires the ability to identify the individuals who are at sufficiently high risk to benefit from screening. Currently, men at elevated risk for breast cancer either present with breast cancer and undergo testing subsequently as survivors, or come to attention via female relatives with breast cancer or through genetic testing showing predisposing mutations. In this select group of patients, multiple risk factors frequently overlap, compounding overall breast cancer risk. For example, approximately 20% of men with breast cancer have a family history of breast cancer; of those with both breast cancer and family history of breast cancer, up to 77% are *BRCA2* mutation carriers and 19% *BRCA1* mutation carriers (38). Compared to average-risk men, whose lifetime risk for breast cancer is approximately 0.1%, *BRCA2* mutation carriers have a lifetime risk of 8%, and *BRCA1* mutation carriers have a lifetime risk of 2% (39). Given that first-degree family history of breast cancer further increases risk for men, which also rises exponentially with increasing number of affected relatives (sister alone, relative risk of 2.25; sister and mother, relative risk of 9.93), it is indeed conceivable that the overall risk of breast cancer in some men may approach that of average-risk women (12%), potentially justifying mammography screening (40). While age is an additional independent risk predictor in men, who typically present with breast cancer later in life than in women (median age, 63) (14), hereditary male breast cancers in *BRCA* mutation carriers are associated with a younger age of onset, with the relative risk of breast cancer being highest for those in their 30s and 40s (41).

Once diagnosed with breast cancer, men are at high risk for developing a second breast cancer. Cancer registry data show that a personal history of breast cancer in men is an independent risk factor and confers a 52- to 93-fold increased risk of subsequent breast cancer compared to their average-risk counterpart (42,43), and this risk appears to be the highest among those with breast cancer diagnosed at a young age (<50 years) (110-fold increased risk) (44).

Breast cancer risk assessment in men is currently less nuanced than in women. There is no standardized risk categorization based on calculated lifetime risk because no validated risk prediction model currently exists for men. However, more consistent genetic testing in women with breast cancer and wider availability of direct-to-consumer

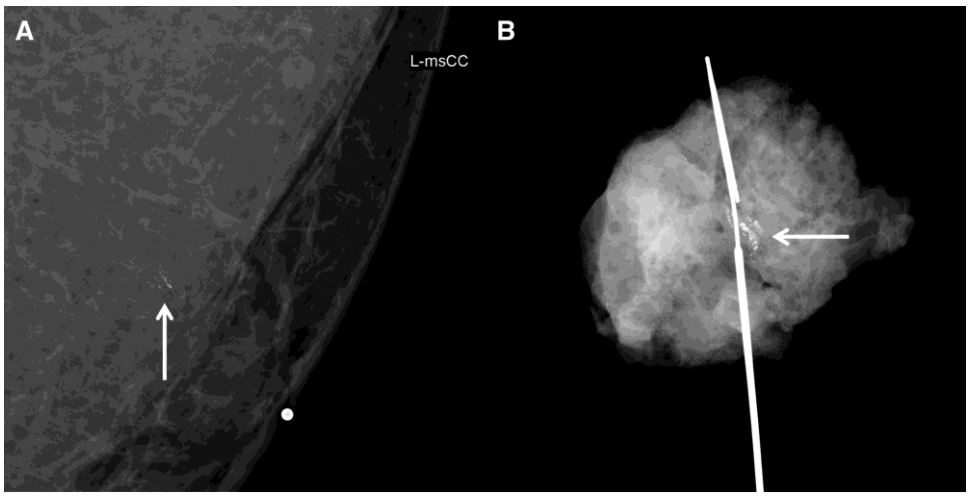

Figure 2. Images of a 53-year-old high-risk male patient, with a strong family history of breast cancer in his father and multiple sisters, who underwent mammography screening. **A:** Left magnification craniocaudal view demonstrates a small group of calcifications (arrow). BB marker is on the nipple. **B:** Wire-localized excisional biopsy was performed, with surgical specimen radiograph confirming inclusion of the targeted calcifications (arrow), yielding pathology result of ductal carcinoma in situ with an invasive component.

genetic testing (eg, 23andMe, 23andMe Holding Co., San Francisco, CA) have provided an opportunity to increasingly identify high-risk individuals. Furthermore, there is a growing body of research confirming a relative prevalence of male breast cancer among African American men disproportionately impacted by worse survival outcomes. Data from the U.S. cancer registry from 2010 to 2016 including 11 990 men with invasive breast cancers showed a 52% higher incidence of breast cancer in Black men than in non-Hispanic White men (45). Men of Ashkenazi Jewish descent comprise another group at elevated risk for breast cancer, due to a high penetrance of founder germline *BRCA* gene mutations (46). Other mutations associated with male breast cancer have been found in *CHEK2*, *PALB2*, and *PTEN* genes, among others (47). Additional risk factors predisposing to male breast cancer include conditions that have excess relative level of estrogen to androgen, such as Klinefelter syndrome, liver disease, or testicular abnormalities, as well as environmental exposures, notably chest or mantle radiation at a young age (1).

Screening Outcomes

Mammography screening has been sporadically utilized in men at elevated risk for breast cancer, and the cancer detection rate (CDR) has been found to be comparable to cancer yield in average-risk women (9,11). In a retrospective study of mammography screening over 7 years in 163 asymptomatic men (77% with personal history of breast cancer and 15% with genetic mutations), four node negative cancers were identified on mammography as new masses (mean size, 6.25 mm; range, 4–7 mm), yielding a CDR of 4.9 per 1000 exams (11). Similarly, in another retrospective study of mammography screening over 12 years in 165 asymptomatic men (13% with personal history of breast cancer and 87% with genetic mutations), five node negative cancers were identified on mammography as either masses (n = 2) (mean size, 11.5 mm; range, 8–15 mm) or calcifications alone (n = 3), yielding a CDR of 18 per 1000 exams, which notably included bilateral screen-detected cancers in a single high-risk patient on consecutive year mammograms (9). In comparison to diagnostically detected cancers in symptomatic men, screen-detected cancers were significantly smaller, more likely to be in situ cancers (60% vs 0%) and seen as calcifications only (60% vs 0%) (Figure 2) (9). Axillary nodal metastasis is a strong prognostic indicator and is present in 58.3% of breast cancer cases in symptomatic men, whereas none of the screen-detected cancers had nodal involvement, suggesting screening has the potential to improve clinical outcomes.

Mammographic sensitivity for cancer is excellent in men because of a relative lack of tissue masking. As in the diagnostic setting, mammography performs exceptionally well in the male breast for screening and has a sensitivity of 100%, specificity of 95%, and NPV of 100% (9). Notably, mammography was the first imaging modality of detection for all screen-detected cancers in men in the two retrospective series, but not all detected cancers were visible on US because of mammographic detection of calcified in situ lesions, validating mammography as an optimal screening modality in the male breast (9,11).

Screening Guidelines

There are no prospective data on male breast cancer screening because screening is not widely adopted in men. Retrospective data have shown, however, that early preclinical detection of male breast cancer is possible through targeted mammography screening in patients who are at elevated risk for breast cancer. Updated guidelines on risk management of male breast cancer reflect a growing interest in leveraging mammography to improve breast cancer outcomes in men, but screening remains controversial because the impact on survival is unknown (Table 2). The 2020 American Society of Clinical Oncology Guideline for Management of Male Breast Cancer currently recommends ipsilateral annual mammogram be offered to men with a history of breast cancer treated with lumpectomy regardless of genetic predisposition, and contralateral annual mammogram *may* be offered to men with a history of breast cancer and a genetic predisposing mutation (48). The 2023 National Comprehensive Cancer Network guideline for men who test positive for *BRCA* mutations currently recommends annual clinical breast exam to start at age 35, and to *consider* annual mammographic screening in men

Table 2. Mammography Screening Guidelines in Men at Elevated Risk for Breast Cancer (45,46)

The 2020 ASCO Guideline for Management of Male Breast Cancer
- Ipsilateral annual mammogram should be offered to men with a history of breast cancer treated with lumpectomy regardless of genetic predisposition
- Contralateral annual mammogram may be offered to men with a history of breast cancer and a genetic predisposing mutation
The 2023 NCCN Guideline for Male BRCA Mutation Carriers
- Annual clinical breast exam starting at age 35 years
- Consider annual mammogram in men with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family, whichever comes first

Abbreviations: ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network.

with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family, whichever comes first (49). Of note, data are mixed in terms of whether presence of gynecomastia is associated with breast cancer development (50,51). Certainly from an imaging perspective, multiple men with screen-detected breast cancers in the retrospective studies had no underlying gynecomastia (9,11).

Other Considerations

Education and awareness are inextricably linked to screening in cancer prevention. In the case of male breast cancer, survey results show that the majority of men with family history of breast cancer (80%) are not aware that men can get breast cancer and that the majority of male *BRCA* mutation carriers (93%) have difficulty reconciling their gender identity with the risk of a cancer perceived as an exclusively woman's disease (52,53). Further barriers include lack of insurance coverage for male breast cancer screening because of limited data and inconsistencies in current guidelines. It is also well demonstrated that men have a tendency to avoid or delay medical care in general, which has a deleterious effect on their health (54,55). In men who present with symptomatic breast cancer, studies have found that they sought care only after a considerable delay (mean duration of symptoms, 10–30 months) (56–58). Therefore, educating the public and improving awareness of male breast cancer is an important first step to improve outcomes.

Conclusion

Breast cancer is a disease of low incidence but high impact in men. Delayed diagnosis adversely impacts survival, despite a more indolent disease molecular profile. Male breast cancer is overwhelmingly ductal in origin and primarily luminal and preceded by DCIS, lending itself to mammographic depiction. The role of imaging in men has been largely to characterize rather than to detect breast cancer. However, targeted mammography screening in men with identifiable risk factors has shown comparable cancer yield to that in average risk women, notably detecting only node-negative disease. Wider and more consistent risk-based screening in men has the potential to help address persistent gender-based survival disparity, but careful patient selection and education are necessary. Society guidelines currently suggest annual mammography in men with *BRCA* mutations starting at age 50 or 10 years before earliest onset of breast cancer in the family, and they recommend annual mammography in male breast cancer survivors, particularly among those with concurrent genetic mutations. While further evidence is needed to support and refine screening recommendations in men, current guidelines can serve as a starting point of consensus and individual conversations about screening. Mammography is widely available and could serve as an integral part of education and risk management in men at high risk for breast cancer.

Funding

None declared.

Conflict of Interest Statement

S.L.H. serves on the *JBI* editorial board. As such, she was excluded from the editorial process. The authors have no other relevant disclosures.

References

Alimkhodjaeva L. T., Kh N. M. RELEVANCE OF DIAGNOSTICS AND TREATMENT OF BREAST CANCER IN MEN. – 2021.

Норбекова М. Х. Прогностическое и предиктивное значение ангиогенеза при раке грудной железы. – 2021.

Kurbankulov U. M. et al. Study of morphological and clinical bases of organpreserving surgery for ampular cancer of the rectum. – 2023.

Alimkhodjaeva L. T. et al. Diagnostic Significance of Molecular Genetic Markers in the Prognosis of the Breast Cancer Clinical Course. – 2019.

Alimkhodjaeva L. T., Norbekova M. H. Clinical significance of the density of tumor microvessels in breast cancer in men. – 2022.

Kh N. M., Zievedenova S. S. TUMOR LYMPHOCYTES IN HER2-POSITIVE BREAST CANCER (Litera review) //Original medicine. – 2023. – Т. 2. – №. 2.

Эргашева Ш. Т. Бухгалтерский учет //Учебное пособие «Иктисод-молия. – 2010.

Tuychieva O., Sh E. Organizational activity as a function of management of the learning process //Актуальные проблемы гуманитарных и естественных наук. – 2016. – №. 3-5. – С. 67-69.

Эргашева Ш. Т. Взаимосвязи системы бухгалтерского и налогового учета. – 2016.

Khalmuratova M. T. PROFESSIONAL LANGUAGE OF DENTIST-DENTISTRY //Экономика и социум. – 2018. – №. 10 (53). – С. 40-42.

Алимходжаева Л. Т. Иммуноморфологические изменения в опухолях молочной железы при неоадъювантной химиотерапии в условиях искусственной гипергликемии //Опухоли женской репродуктивной системы. – 2008. – №. 2. – С. 35-37.

Alimkhodjaeva L. T., Kh N. M. RELEVANCE OF DIAGNOSTICS AND TREATMENT OF BREAST CANCER IN MEN. – 2021.

ZAKIROVA L. T., TelmanovnaALIMKHODJAEVA L., KADYROVA D. A. Chromosomal Disorders and Aberrant DNA Methylation as Early Biomarkers of Breast Cancer Risk in Young Women //Journal of Life Science and Biomedicine. – 2018. – Т. 8. – №. 1. – С. 01-05.

Алимходжаева Л. Т. Диагностическое значение

изучения уровней про-и противовоспалительных цитокинов иммунной системы у больных раком молочной железы //Опухоли женской репродуктивной системы. – 2009. – №. 3-4. – С. 49-52.
Алимходжаева Л. Т. Диагностическое значение изучения уровней про-и противовоспалительных цитокинов иммунной системы у больных раком молочной железы //Опухоли женской репродуктивной системы. – 2009. – №. 3-4. – С. 49-52.