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Pancreatic Cancer

Includes 9 Pharmacotherapeutic/Pharmacology Hours

Audience
This course is designed for nurses, advanced practice nurses, and other members of the interprofessional healthcare team involved in the care of patients with pancreatic cancer.

Course Objective
The purpose of this course is to provide healthcare professionals with the knowledge and skills necessary to recognize and appropriately manage pancreatic cancer in their patients.

Learning Objectives
Upon completion of this course, you should be able to:

1. Outline the epidemiology of and risk factors for pancreatic cancer.
2. Describe the pathophysiology of pancreatic cancers.
3. Discuss recommendations for screening for pancreatic cancer in various patient populations.
4. Describe key aspects of the clinical evaluation of patients with suspected pancreatic cancer.
5. Select the appropriate tools for diagnosis and staging of pancreatic cancer.
6. Apply models of assessing the functional performance status of patients with diagnosed pancreatic cancer.
7. Discuss the role of resection in pancreatic cancer treatment, including most appropriate approaches.
8. Compare and contrast chemotherapy regimens used in the treatment of pancreatic cancer.
9. Describe the use of radiation therapy as a component of pancreatic cancer treatment according to evidence-based guidelines.
10. Evaluate available interventions to manage symptoms and provide palliative care to patients with pancreatic cancer.

Faculty
Mark Rose, BS, MA, LP, is a licensed psychologist in the State of Minnesota with a private consulting practice and a medical research analyst with a biomedical communications firm. Earlier healthcare technology assessment work led to medical device and pharmaceutical sector experience in new product development involving cancer ablative devices and pain therapeutics. Along with substantial experience in addiction research, Mr. Rose has contributed to the authorship of numerous papers on CNS, oncology, and other medical disorders. He is the lead author of papers published in peer-reviewed addiction, psychiatry, and pain medicine journals and has written books on prescription opioids and alcoholism published by the Hazelden Foundation. He also serves as an Expert Advisor and Expert Witness to law firms that represent disability claimants or criminal defendants on cases related to chronic pain, psychiatric/substance use disorders, and acute pharmacologic/toxicologic effects. Mr. Rose is on the Board of Directors of the Minneapolis-based International Institute of Anti-Aging Medicine and is a member of several professional organizations.

Faculty Disclosure
Contributing faculty, Mark Rose, BS, MA, LP, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has the worst prognosis of any common cancer. The five-year overall survival rate is approximately 10% and has improved only marginally in five decades [1]. There are four fundamental challenges that underlie the high mortality of PDAC: pancreatic anatomy, aggressive biology, systemic effects, and treatment resistance.

The retroperitoneal position of the pancreas is situated deep within the upper abdomen, behind the stomach, and between the aorta and its major upper abdominal branches. Shielded from detection, the tumors often grow around and encase these vessels, making the cancer inoperable in nearly 85% of patients [2]. With this aggressive cancer, more than 50% of patients have distant metastases at diagnosis, and micrometastases are already present in most patients undergoing resection for apparently localized tumors [2; 3; 4].

At diagnosis, up to 80% of patients with PDAC present with cachexia, a wasting syndrome and physiologic effect of PDAC. Cachexia dramatically weakens patients, limiting their ability to withstand aggressive treatment. The poor treatment tolerance of patients with cachexia is evidenced by decreased survival after resection or chemotherapy [2].

The complex tumor microenvironment and heterogeneity of gene mutations make PDAC one of the most drug-resistant cancers. Most treatment options are ineffective, with rapid progression and low complete responses to the most effective chemotherapy and radiotherapy [1; 4].

Surgical resection of the pancreas with microscopically free margins (R0 resection) followed by chemotherapy remains the only realistic option for remission, but this is potentially achievable in only a fraction of patients [4; 5]. Nonetheless, incremental gains have been increasingly frequent over the past decade, and more substantive gains are anticipated, pending clinical trial results. This course will describe the current standard of care for patients with pancreatic cancer and present information that may help increase earlier detection of this malignancy and improve the symptom burden and quality of life in these patients, regardless of disease stage.

Clinical practice guidelines for patients with pancreatic cancer have been published by the American Society of Clinical Oncology (ASCO), the NCCN (National Comprehensive Cancer Network), the American Society for Radiation Oncology (ASTRO), the European Society for Medical Oncology (ESMO), the National Institute for Health and Care Excellence (NICE), and others [6; 7; 8; 9; 10; 11; 12; 13; 14; 15]. The recommendations are largely concordant on what constitutes multidisciplinary standards of care in the management of pancreatic cancer [2; 16].

Most pancreatic cancers arise in the exocrine pancreas (95%). Tumors of the endocrine pancreas (<5%) are distinct from exocrine pancreas cancers and will not be discussed in this course [4].

PDACs account for more than 95% of exocrine pancreatic cancers. PDAC and pancreatic cancer are commonly used as interchangeable terms in the literature and will be in this course [17].

EPIDEMIOLOGY

What is the median age at diagnosis of pancreatic cancer?

During 2021 in the United States, an estimated 60,430 people will be diagnosed with pancreatic cancer, which represents 3.2% of all new cancer cases and the 11th most common new cancer diagnosis. The median age at diagnosis is 70 years [18].

Approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime, based on 2016–2018 data. In 2018, an estimated 83,777 people were living with PDAC in the United States [19].

With an estimated 48,220 deaths in 2021, pancreatic cancer is the third leading cause of cancer death (after lung and colorectal cancer) in both men and women; it is expected to become the second leading cause of cancer death by 2030 [2; 19; 20]. The median age at death is 72 years [18].

Pancreatic cancer stage at diagnosis strongly influences the length of survival, as shown by data from 2011 to 2017 (***Table 1***) [19]. The five-year survival of PDAC, 10.8%, remains the lowest of all common cancers [19; 21].

During 2013–2017, annual pancreatic cancer incidence and mortality rates (per 100,000 persons) were higher among men (14.9 and 12.7) than women (11.6 and 9.6). These rates were highest for Blacks (15.3 and 13.3), followed by non-Hispanic Whites (13.1 and 10.9) and Hispanics. The rates were lowest for Asian/Pacific Islanders and American Indian/Alaska Natives [2].

Since 2010, both incidence and mortality rates increased by an average of 0.3% per year. Underlying these trends is a combination of an aging population, a longer lifespan, and the high prevalence of obesity and diabetes [11; 18]. In 2015, lost earnings from person-years of life lost from pancreatic cancer were estimated at more than $6 billion [2].

PANCREATIC CANCER STAGE AT DIAGNOSIS AND ASSOCIATED SURVIVAL		
Stage	**Progression at Diagnosis**	**Five-Year Survival**
Localized	11%	41.6%
Regional	30%	14.4%
Distant	52%	3.0%
Unknown	7%	6.5%
Source: [19]		*Table 1*

RACIAL SURVIVAL DISPARITIES

In examining PDAC survival disparities over 2004–2015, the unadjusted median overall survival was slightly longer for White patients than Black patients (6.6 months vs. 6.0 months). Decreased survival for Black patients persisted after controlling for sociodemographic parameters. Conversely, controlling specifically for clinical parameters (e.g., disease stage, treatment) found a modest survival advantage for Black patients [22].

Black patients with PDAC present at younger ages with more advanced disease than White patients, possibly suggesting differences in tumor biology. Black patients receive less treatment stage-for-stage and fewer surgeries for resectable PDAC than White patients; these findings may be only partly associated with socioeconomic differences. In one study, when disease stage and treatment were controlled for, Black patients had no decrease in survival compared to other races [22].

Role of Implicit Bias

Health professionals' implicit biases shape behaviors, communications, and interactions, which then produce differences in diagnoses and ultimately treatments and interventions. Implicit biases are subtle and unconscious and may unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider.

Racial and socioeconomic differences in surgical intervention rates, treatment at high-volume hospitals/centers, and morbidity and mortality rates have been noted, with the largest disparities between Black (and to a slightly lesser extent Hispanic) and White Americans [23]. Several factors are implicated, but implicit biases and insurance status are identified as potentially modifiable contributors.

NON-GENETIC RISK FACTORS

The most common recognized risk factor for pancreatic cancer is cigarette smoking followed by obesity. Others include pancreatitis, diabetes, and family history of pancreatic cancer (***Table 2***) [13; 24]. Periodontal disease is increasingly linked to pancreatic and other gastric cancers. Chronic pancreatitis substantially elevates the risk of developing pancreatic cancer and represents an opportunity for surveillance and monitoring. Most importantly, new-onset hyperglycemia or diabetes is now recognized as an early symptom of PDAC in an otherwise asymptomatic patient. Many recognized risk factors are modifiable for prevention of pancreatic cancer.

COMMON RISK FACTORS FOR THE DEVELOPMENT OF PANCREATIC CANCER	
Factor	**Relative Risk**
Cigarette smoking	1.7-fold to 2.6-fold
Obesity	1.1-fold to 1.5-fold
Diabetes	1.5-fold to 2-fold
Family history	1.7-fold to 2.3-fold
Chronic pancreatitis	13.3-fold
Source: [2]	*Table 2*

Smoking

Cigarette smokers have at least a two-fold greater risk for pancreatic cancer than nonsmokers. The risk increases with the amount of cigarettes consumed and duration of smoking. In heavy smokers with polymorphism in the carcinogen-metabolizing enzyme gene glutathione S-transferase theta 1 (*GSTT1*), the risk is up to five-fold greater [25; 26].

Excess risk decreases with smoking cessation. The risk of pancreatic cancer among current smokers (relative risk: 2.5) decreased 48% two years after smoking cessation, and within 10 to 15 years after cessation, it approximated that of nonsmokers [26].

In the United States, estimates indicate that 11% to 32% of deaths from PDAC are attributable to tobacco smoking. It is estimated that cessation of smoking could eliminate up to 25% of pancreatic cancer deaths [24; 26].

Alcohol Consumption

Limited evidence suggests alcohol consumption may be associated with risk of developing PDAC, but findings of population-based studies are inconsistent. In pooled cohort data of 1.5 million light, heavy, or never-drinkers, heavy drinkers had a greater relative risk of developing PDAC than never-drinkers (relative risk: 1.29) or light drinkers (relative risk: 1.36). Light drinkers had no difference compared to never-drinkers (relative risk: 0.96) [27].

Smoking and Drinking

Most studies have assumed additivity between average effects of smoking and alcohol and oversimplified their impact on burden of pancreatic cancer. However, the combined effect of smoking and total alcohol intake on risk of PDAC is likely non-additive. It appears that only heavy consumption of liquor (but not wine or beer) increases the risk of PDAC in ever-smokers [27].

Obesity

A number of studies have associated obesity with a higher incidence of pancreatic cancer. Obesity (defined as a body mass index [BMI] >30) during early adulthood was associated with a greater risk of PDAC and younger age of disease onset. Tumorigenesis is enhanced by excess adipose tissue. Obesity is associated with a 20% to 40% higher mortality rate from PDAC, and obesity at an older age is associated with lower overall survival [13; 28].

Although BMI is widely used as a marker for general adiposity, visceral obesity has a stronger correlation to metabolic syndrome, insulin resistance, and certain gastrointestinal (GI) malignancies. The close proximity to visceral organs and drainage via the portal system may explain the strong correlation of inflamed visceral adipose tissue (VAT) in obese subjects with metabolic dysfunction and pancreatic cancer [29].

Diet

There is some evidence that higher consumption of red/processed meat is associated with elevation in pancreatic cancer risk, but other studies have failed to identify dietary risk factors for PDAC [11]. Pancreatic cancer incidence may be lower in persons with higher intake of fresh fruits and vegetables rich in folate and lycopenes (e.g., tomatoes) [30].

A link between vitamin D and risk for pancreatic cancer is inconsistent, but some data suggest low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer, especially in those with low retinol/vitamin A intake [31]. Coffee and tea consumption are not associated with pancreatic cancer risk, despite early reports to the contrary [24].

Systemic/Nonmodifiable Risks

Numerous studies and meta-analyses have found systemic/nonmodifiable factors that increased the relative risk, hazard ratio, or odds ratio of developing pancreatic cancer. These include individuals with greater height (relative risk: 1.81); individuals with blood groups A, AB, and B (hazard ratio: 1.32, 1.51, and 1.72, respectively); and patients with hepatitis B infection (odds ratio: 1.50) or systemic lupus erythematosus (hazard ratio: 1.43). Biologic explanations for some of these associations are not yet understood, and some data may have potential confounders. Infectious etiologies warrant more investigation [11; 32].

Periodontal Disease

Periodontitis describes a chronic inflammatory response to a disease-associated, multispecies bacterial community in the subgingival region. Periodontal disease is associated with pancreatic cancer, even when controlling for gender, smoking, BMI, diabetes, and alcohol consumption [33]. The inflammatory processes of periodontitis occur locally, but systemic dissemination of inflammatory mediators, subgingival species, and bacterial components contribute to digestive cancers (including PDAC) by activating proinflammatory pathways, inducing gene expression related to cell proliferation, apoptosis, and immune responses linked to carcinogenesis, cell migration, invasion, and metastasis [34].

Chronic Pancreatitis

A high-risk subgroup for PDAC are patients with chronic pancreatitis, often secondary to chronic alcohol use disorder, smoking, hypertriglyceridemia, diabetes, or renal failure [2]. Patients with chronic pancreatitis show a 26-fold increase in risk of developing PDAC. This risk increases with duration. Among patients with chronic pancreatitis of 20 years' duration, approximately 5% will progress to PDAC.

Concomitant smoking enhances the risk of neoplastic progression [2; 35]. Hereditary pancreatitis further increases the risk of pancreatic cancer by more than 50-fold. In these individuals, the cumulative risk of pancreatic cancer by age 70 years is 40% [24].

Long-Standing Diabetes

Pancreatic cancer has complex relationships with diabetes and obesity that are only recently becoming understood. A population cohort study underscored the complex relationship between metabolic abnormalities and PDAC. Glycemic status, insulin resistance, and hyperinsulinemia were independently associated with an increased risk of pancreatic cancer mortality, even in individuals without diabetes [36].

The association between pancreatic cancer and diabetes was noted as early as 1833, clearly documented by the 1930s, and characterized in a large cohort of patients with pancreatic cancer from Mayo Clinic in 1958 [37]. Several meta-analyses have greatly refined the risk-factor status of diabetes.

Long-standing (i.e., more than five years) diabetes (both type 1 and type 2) is associated with increased risk of developing PDAC [13]. The overall risk for PDAC increases 4- to 7-fold in those with diabetes of a duration less than three years [38]. The relative risk associated with diabetes levels off after five years, with a 1.5-fold greater risk [39]. Increased baseline hemoglobin A1C (HbA1C) levels correlate with subsequent development of PDAC [40].

Long-standing diabetes modestly increases the risk of PDAC, which decreases with diabetes duration [11; 37]. The initial three-year period after diabetes diagnosis is high risk for PDAC, as confirmed by prospective pancreatographic screening [41].

With diabetes medications, insulin use has been associated with increased risk of PDAC, but this finding is attributed to reverse causality [11; 42]. Metformin use in patients with diabetes and PDAC was associated with improved two-year survival (30.1% vs. 15.4%) and median overall survival (15.2 months vs. 11.1 months) in patients without metastases [43]. One metformin study reported negative findings [44].

Long-standing diabetes in patients who develop PDAC is associated with significantly lower overall survival (14.4 months vs. 21.7 months) and significantly higher mortality (harm ratio: 1.52) compared with patients without diabetes who develop PDAC [11; 45].

Postpancreatitis Diabetes Mellitus

Diabetes of the exocrine pancreas (formerly type 3c diabetes) is the second most common type of new-onset diabetes in adults (behind type 2 diabetes) [42]. Acute or chronic pancreatitis is one of the most prevalent risk factors for PDAC and the most frequent cause of diabetes of the exocrine pancreas. Pancreatitis leads to postpancreatitis diabetes mellitus in up to 83% of patients [42]. In a registry study involving 139,843 individuals, the proportion of pancreatic cancer was 3.1% among those with postpancreatitis diabetes mellitus, compared with 2.3% in those with type 2 diabetes followed by pancreatitis, 2.0% in those with pancreatitis alone, and 0.6% in individuals with type 2 diabetes alone [42].

Prediagnostic Metabolic and Soft Tissue Changes

Numerous studies have identified new-onset diabetes, weight loss, and soft tissue changes in patients with PDAC at diagnosis, but their inter-relationship and connection to PDAC remained unaddressed. From 2000 through 2015, temporal changes in the five years preceding PDAC diagnosis of 219 patients diagnosed with PDAC were compared to 657 controls [46]. From 60 to 30 months before PDAC diagnosis, patients did not significantly differ from controls. However, starting at 30 months prediagnosis, PDAC showed three distinct metabolic phases, each marked by onset and significant progressive worsening of one or more metabolic abnormalities [46]:

- Phase 1, hyperglycemia (30 to 18 months before PDAC diagnosis): A significant proportion of patients develop hyperglycemia, without soft tissue changes.
- Phase 2, pre-cachexia (18 to 6 months before PDAC diagnosis): Decreases in serum lipids, weight loss, and the first soft tissue change (subcutaneous abdominal tissue loss) are seen. A profile appears of advanced prediabetes (i.e., fasting blood glucose 120–126 mg/dL or A1c of 6% to 6.5%). In type 2 diabetes, this is associated with weight gain and hyperlipidemia due to insulin resistance. In PDAC, decreases in weight and serum lipids despite rising glucose levels are paradoxical.
- Phase 3, cachexia (less than 6 months before PDAC diagnosis): Onset of muscle loss, visceral adipose tissue loss, and decreasing high-density lipoprotein. Continued decreases in all other serum lipids, subcutaneous abdominal tissue, and weight. Fasting blood glucose continues rising.

Based on evidence of increases in body temperature before PDAC diagnosis, browning and loss of subcutaneous abdominal tissue is estimated to begin 18 months before PDAC. Browning of white abdominal tissue is a mechanism of subcutaneous abdominal tissue loss in cancer; its purpose is to generate heat [46].

Symptoms of cachexia and muscle loss (e.g., anorexia, fatigue, reduced exercise tolerance) appear shortly (less than six months) before PDAC diagnosis. The onset of objective weight loss precedes PDAC diagnosis by one year or more. New-onset diabetes appears a median of six to nine months before PDAC diagnosis [46].

Pancreatic Cancer Cachexia and Diabetes

Cancer cachexia is a paraneoplastic syndrome characterized by pronounced weight loss and muscle wasting triggered by cancer-induced systemic inflammation [47]. Cachexia develops in about 80% of patients with PDAC during the disease course, often before the tumor is clinically apparent. Cachexia negatively impacts treatment response and survival, and one-third of patients with PDAC die from cachexia-associated complications, including impaired immunity and cardiopulmonary dysfunction. No curative treatments exist [47].

Pancreatic cancer-associated diabetes mellitus might be a major contributor to PDAC-induced cachexia. The co-occurrence is frequent, and the relationship between pancreatic cancer-associated diabetes and PDAC-induced cachexia was clarified in a 2020 study [47]. Compared with patients without pancreatic cancer-associated diabetes, those with pancreatic cancer-associated diabetes did not have a higher risk of cachexia, a greater degree of weight loss, or lower skeletal muscle mass. Among patients with cachexia, weight loss and skeletal muscle mass were comparable between patients with and without pancreatic cancer-associated diabetes. Fasting blood glucose levels and PDAC-derived diabetogenic factors did not correlate with weight loss or muscle mass or predict cachexia in patients with pancreatic cancer-associated diabetes. A notable finding was the consistently high prevalence of cachexia and muscle wasting regardless of tumor size and stage in PDAC [47]. These results argue against pancreatic cancer-associated diabetes and hyperglycemia in mediating PDAC-induced cachexia.

Cancer cachexia is characterized by systemic inflammation with resultant skeletal muscle breakdown and increased circulating amino acids to support tumor growth. Pancreatic cancer-associated diabetes is a metabolic strategy by PDAC to fuel tumor growth. PDAC cells have a high demand for glucose (termed "glucose addiction"); hyperglycemia promotes invasion and migration of PDAC cells. PDAC-induced cachexia and pancreatic cancer-associated diabetes are distinct metabolic reprogramming induced by PDAC cells to secure amino acids and glucose for tumor growth [47].

Unexplained weight loss/cachexia is a clue to occult PDAC, but a modality that can identify PDAC-induced cachexia is needed to take advantage of this screening opportunity [47]. Optimizing glycemic control may not alleviate weight loss or muscle wasting, and therapies targeting mediators of pancreatic cancer-associated diabetes may not protect against the development of cachexia [47]. Management of cachexia in patients with PDAC is discussed in detail later in this course.

PATHOPHYSIOLOGY

PDAC is caused by somatic (acquired) and germline (inherited) mutations in specific cancer-associated genes. In PDAC, the accumulation of multiple combinations of gene mutations significantly perturbs major signaling pathways, leading to a malignant phenotype [13; 48; 49; 50].

Like most solid tumors, PDACs are driven by mutations that disrupt intra- and extracellular networks that normally restrain abnormal growth, proliferation, survival, and invasion [51]. Four major genetic drivers are fundamental in nearly all PDACs. These involve mutational activation of the oncogene *KRAS*, and mutational inactivation of the tumor suppressor genes *CDKN2A*, *TP53*, and *SMAD4* [3; 50; 52; 53]. Inactivation of genome maintenance genes that repair DNA damage is a third broad type of mutation in PDAC.

PRIMARY MUTATIONAL DRIVERS IN PDAC

KRAS encodes a GTPase molecule that acts as a transducer for growth factor receptors on the cell surface. *KRAS* mutations dysregulate intrinsic GTPase activity, stimulating downstream pathways that drive uncontrolled cellular proliferation, angiogenesis, suppression of apoptosis, and evasion of immune response [54].

CDKN2A encodes the proteins p16 and p14ARF, which are both cell-cycle regulators. With loss of *CDKN2A* gene function, inactivation of p16 results in unchecked cell cycle progression and enhanced tumor cell proliferation [3; 49]. *TP53* encodes the protein p53, called the "guardian of the genome," which plays a central role in DNA repair, cell cycle arrest, and induction of apoptosis in response to DNA damage or cellular stress [55].

Inactivation of p53 (loss of function mutation) allows DNA damage to go unchecked with failed apoptosis and unregulated G1/S cell cycle transition. Mutant p53 can also gain pro-oncogenic activities (gain-of-function mutation), promoting cell proliferation, survival, angiogenesis, and metastases [54].

SMAD4 encodes the protein Smad4, a downstream effector of transforming growth factor-beta (TGF-b) signaling pathway. *SMAD4* inactivation and loss of Smad4 promotes cancer progression by removing the early growth inhibitory effect of the TGF-b pathway and is associated with higher rates of distant metastasis and poorer prognosis [54].

MUTATIONAL SEQUENCE OF PDAC DEVELOPMENT

What are the most common precancerous precursor lesions associated with pancreatic cancer?

Through pathways and somatic mutations that differ modestly in each lesion, PDAC develops from precancerous precursor lesions: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasms (MCNs). The most common are PanINs (approximately 90%), and the least common are MCNs. However, all precursor lesions have key similarities [4; 48; 50]:

- Early oncogene mutations initiate tumorigenesis.
- Later loss of tumor suppressor genes drive tumor progression, high-grade dysplasia, and invasive cancer.
- Increasing grades of dysplasia are associated with accumulation of somatic mutations in key driver genes.

Pancreatic Intraepithelial Neoplasia (PanIN)

PDAC develops in PanINs through a specific process [56]. First, mutational *KRAS* activation initiates pancreatic carcinogenesis. With tumor suppressor inactivation, cancer progresses. *CDKN2A* or *SMAD4* are implicated in locally destructive disease; *TP53* is involved in metastatic seeding; and concurrent *SMAD4* and *TP53* are often present in locally or metastatic dominant disease. IPMNs and MCNs often share the driver gene mutations and sequence of PanINs, but also show specific patterns.

Intraductal Papillary Mucinous Neoplasms (IPMN)

More than 90% of IPMNs are marked by activating mutations in the oncogene *GNAS* and/or inactivating mutations in the tumor suppressor gene *RNF43* [48; 53; 54]. *GNAS* mutation causes constitutive activation of adenylyl cyclase, with downstream effects driving proliferation. *RNF43* encodes E3 ubiquitin-protein ligase, which functions as a tumor suppressor in the Wnt-signaling pathway. After the initiating oncogene mutation, the progression of IPMN resembles PanIN.

Mucinous Cystic Neoplasms (MCN)

RNF43 mutation is also a prevalent event in MCNs (50%). As in PanINs, genetic changes accumulate with higher grade of dysplasia and invasiveness [48; 53; 54].

NATURAL HISTORY OF PDAC ONCOGENESIS

The PanIN Progression Model has been critical in shaping the perspective of how PDAC develops and progresses over the past two decades. PDAC arises through a specific sequence of genetic alterations over a gradual progression from early PanIN to late-stage metastatic disease [57; 58; 59].

The timeframe of PanIN progression has also been established. Based on computational modeling using autopsy cases, the estimated average time interval from initiation in normal cells to invasive ability (11.7 years), metastatic dissemination (6.8 years) and death (2.7 years) corresponds to an average of about 21 years from the initiating mutation until a patient's death [17].

Most cases with PDAC are diagnosed toward the end of this lifetime span, suggesting that poor prognosis is a result of late diagnosis in the natural history of PDAC, and that a golden opportunity of two or three years exists to diagnose "early" pancreatic cancer (i.e., Stage 0 or I) [60].

Chromothripsis, a recently identified phenomenon, is a catastrophic event causing tens to thousands of chromosomal rearrangements. Faced with hundreds of DNA breaks, the cell's DNA repair machinery attempts to rescue the genome, but the result bears little resemblance to its original structure [61; 62]. This genomic disruption can drive the development of cancer through DNA copy number changes, including deletion of tumor suppressor genes and increased copy number (amplification) of oncogenes [61].

A 2016 study of more than 100 whole genomes from pancreatic cancer tumors found evidence of at least one chromothripsis event in 65% of tumors, and most copy-number changes seemed to occur after such catastrophic genetic events. With evidence of chromothripsis in some PDACs and nongradual tumorigenesis that defies the established mutational sequence, a punctuated equilibrium model was proposed, dividing tumor development into two major events [63]:

- A cancer-initiating event: PDAC pre-neoplasms acquire extensive mutation burden but remain non-invasive over a prolonged preneoplastic phase.
- A cataclysmic cancer-transforming event: Chromothripsis induces DNA copy number changes, creating genomic instability and generating invasive clones with rapid dissemination and colonization of distant sites. Why chromothripsis occurs in PDAC is not yet understood.

Non-Genetic Mechanisms

Rather than being uniformly aggressive, PDAC demonstrates clinical (e.g., variable patient survival) and disease (e.g., variable chemotherapy sensitivity) heterogeneity [64; 65]. The first whole-genome description of PDAC in 2008 prompted great effort to advance a patient-tailored precision medicine approach that could better address this heterogeneity. Genetic alterations and molecular subtypes in PDAC were characterized and published. PDAC was shown mutationally dominated by the four driver genes and homogeneous. In general, the findings importantly informed the biology and familial predisposition of PDAC.

However, by 2019 it was apparent that PDAC disease heterogeneity cannot be explained by genetic mutations alone, and non-genetic mechanisms, including epigenetics and the tumorigenic microenvironment, were the path forward [21; 56; 59; 62; 64; 65; 66; 67].

Epigenetic Factors

Broadly speaking, epigenetic changes influence gene expression, without altering the DNA sequence, through modifications of DNA or chromatin structures [4]. In PDAC, these include: DNA methylation and non-coding RNAs (ncRNAs).

Gene expression in PDAC can be silenced through non-mutational inactivation by aberrant promoter methylation, including the driver gene *p16/CDKN2A* [49]. Aberrant ncRNA expression plays a considerable role in initiation, proliferation, and chemo-resistance of PDAC. Oncogenic microRNA-21 promotes both cell proliferation and apoptosis and targets negative regulators of *KRAS*, which further enhances signaling by this oncogene [50; 54].

PANCREATIC CANCER SUSCEPTIBILITY SYNDROMES AND MUTATIONS	
Category	**Specific Syndromes and Germline Mutations**
Gastrointestinal tract cancers	Lynch syndrome, also termed hereditary nonpolyposis colorectal cancer (*MLH1*, *MSH2*, *MSH6*, *PMS2*) Peutz-Jeghers syndrome (*STK11/LKB1*) Familial adenomatous polyposis (*APC*)
Solid tumor cancers	Hereditary breast/ovarian syndrome (*BRCA1/2*, *PALB2*) Familial atypical multiple mole melanoma syndrome (*CDKN2A*) Li-Fraumeni syndrome (*TP53*)
Chronic pancreatitis-associated syndromes	Hereditary pancreatitis (*PRSS1*, *SPINK1*) Cystic fibrosis (*CFTR*)
Neurodegenerative disease	Ataxia-telangiectasia (*ATM*)
Source: [48; 54]	*Table 3*

Pancreatic Tumor Microenvironment

Pancreatic cancer tissue is comprised of PDAC cells and dense fibrotic stromal (stellate) cells. The stroma consists of extracellular matrix and non-neoplastic (e.g., fibroblastic, vascular, immune) cells [3]. Also described as PDAC fibrosis, the stroma makes up most of the tumor mass. Its importance beyond a physical barrier to drug penetration was not historically considered. Recognized only recently, the entire neoplastic tissue, both tumor cells and stroma, create a pancreatic tumor microenvironment that crucially facilitates PDAC growth, survival, and treatment failure [21; 51; 68].

Pancreatic cancer progresses in tandem with a stromal reaction, characterized by extensive deposition of extracellular matrix, recruitment and activation of cancer-associated fibroblasts, and high interstitial fluid pressures that compress blood vessels, causing hypoperfusion, hypovascularity, and hypoxia [21; 69]. Extracellular matrix remodeling biomechanically induces intracellular signaling and tumor-stellate cell crosstalk. PDAC cells signal to stellate cells and recruit macrophages and immune suppressor cells. In turn, stellate cells secrete factors that promote PDAC cell proliferation and migration and suppress apoptosis [51]. Biochemical activation of signaling pathways that regulate PDAC cell survival and metastasis promotes tumor growth, immunosuppression, disease progression, epithelial-mesenchymal transition (a key step of the metastatic cascade) and invasive potential, and chemotherapy resistance [3; 21; 69].

Exosomes (a macromolecule involved in RNA degradation) released by PDAC cells accumulate in other tissues to create a premetastatic niche by activating stellate cells and inducing remodeling of the host extracellular matrix, which facilitates cancer cell invasion and growth [59; 69].

HEREDITARY PDAC

In addition to the somatic mutations driving pancreatic tumorigenesis in all PDACs, specific germline variants also contribute to PDAC in some patients [48]. In many of these germline mutations, the oncogenic mechanism involves inactivation of DNA damage repair genes [49].

There are two broad categories of inherited risk for PDAC [26; 70; 71]:

- Genetic predisposition or hereditary pancreatic cancer: Germline mutations in PDAC susceptibility genes are present.
- Familial pancreatic cancer: Familial clustering of PDAC (i.e., at least one pair of affected first-degree relatives) without known germline mutations

Sporadic PDAC is when both factors are absent. However, mutations in known pancreatic cancer susceptibility genes are found in 5% to 10% of patients with apparently sporadic pancreatic cancer.

Inherited Cancer Susceptibility Syndromes and Germline Mutations

Several genetic syndromes are associated with specific genetic alterations with an increased risk for pancreatic cancer (***Table 3***) [48; 54]. Germline mutations in familial atypical multiple mole melanoma syndrome (*CDKN2A*) and Li-Fraumeni syndrome (*TP53*) are core gene drivers in sporadic PDAC. Peutz-Jeghers syndrome is caused by germline inactivation of *STK11*, a tumor suppressor gene. Somatic *STK11* mutations are observed in approximately 4% of pancreatic cancers, suggesting *STK11* inactivation plays a role in both sporadic and familial forms [49].

PANCREATIC CANCER RISK IN PREDISPOSITION AND INHERITED CANCER SYNDROMES				
Syndrome	**Gene(s)**	**Risk of PDAC**		**Other Cancers**
		Relative	**Lifetime**	
General population	–	1	0.5%	–
Hereditary breast/ovarian cancer	*BRCA1*	2 to 3	1.2% to 2%	Breast, ovarian, prostate
	BRCA2	3.5 to 10	2% to 10%	
	PALB2	15	5% to 10%	
Familial atypical multiple mole melanoma	*CKDN2A*	13 to 36	10% to 30%	Melanoma
Peutz-Jeghers	*STK11*	75 to 125	11% to 66%	GI, lung, breast, reproductive
Hereditary nonpolyposis colon cancer (Lynch II)	*MLH1, MSH2, MSH6*	8 to 10	3.7% to 10%	Colorectal, ovary, uterine, upper GI, urinary tract
Li-Fraumeni	*TP53*	7	unknown	Breast, brain, adrenal
Familial adenomatous polyposis	*APC*	4.5	Less than 5%	Colon, upper GI, thyroid, brain
Ataxia telangiectasia	*ATM*	8 to 9	1% to 5%	Breast, prostate
Hereditary pancreatitis	*PRSS1, SPINK1*	50 to 82	25% to 44%	–
Cystic fibrosis	*CFTR*	5	Less than 5%	–
Familial pancreatic cancer[a]	1 first-degree relative	4.6	–	–
	2 first-degree relatives	6.4	–	–
	3 first-degree relatives	32	–	–
[a]Risk determined by number of affected first-degree relatives rather than specific gene.				
Source: [49; 54; 70; 73]				*Table 4*

Familial Pancreatic Cancer

An estimated 10% to 15% of all pancreatic cancers are attributable to genetic causes. Pancreatic cancer aggregates in some families; 5% to 10% of individuals with pancreatic cancer have a family history of the disease [26; 70; 72]. Familial pancreatic cancer represents 90% of all hereditary PDAC cases. The relative risk of PDAC increases with the number of affected first-degree relatives.

A specific gene defect responsible for familial pancreatic cancer has not been identified, but a rare autosomal-dominant gene may be responsible, putting 0.4% to 0.7% of the population at risk for developing PDAC [26; 70; 72]. Details about the relative and lifetime risks of PDAC, and the other prevalent cancers associated with specific germline mutations in cancer susceptibility syndromes and familial pancreatic cancer, are summarized in ***Table 4***.

PANCREATIC CANCER SCREENING

With the low population incidence of PDAC (lifetime risk: 1.3%), absence of biomarker screening targets, and high cost of sensitive imaging methods, the U.S. Preventive Services Task Force recommended against screening for pancreatic cancer in asymptomatic adults in 2019, reaffirming its previous conclusion in 2004 [74]. As population screening to achieve earlier detection and intervention of PDAC is not currently feasible, other approaches for this objective have been identified.

In Australia, public awareness campaigns have highlighted the often vague symptoms of PDAC and encouraged individuals to seek medical attention early. Underscoring this point, one study found that many people who were ultimately diagnosed with PDAC were falsely reassured by the subtle, intermittent nature of their symptoms over the preceding months [75; 76].

INTERNATIONAL CANCER OF THE PANCREAS SCREENING (CAPS) CONSORTIUM CONSENSUS ON SCREENING FOR PANCREATIC CANCER IN PATIENTS WITH INCREASED RISK FOR FAMILIAL PANCREATIC CANCER

What is the goal of pancreatic surveillance?

The primary goal is to prevent the emergence of and death from pancreatic cancer by identifying and treating stage I pancreatic cancer (resected with negative margins) and pancreatic cancer precursor lesions with high-grade dysplasia (PanIN or IPMN).

Who should be screened?

All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* mutation)

All carriers of a germline *CDKN2A*(p16) mutation

Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least one affected first-degree relative

Individuals with at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)

At what age[a] should pancreatic surveillance begin?

Familial pancreatic cancer kindred	Start at 50 or 55 years of age, or 10 years younger than the youngest affected blood relative
Mutation carriers	For *CDKN2A* and Peutz-Jeghers syndrome, start at 40 years of age
	For *BRCA2*, *ATM*, *PALB2*, *BRCA1*, and *MLH1/MSH2*, start at 45 or 50 years of age, or 10 years younger than the youngest affected first-degree relative

What tests and indications?

Indication	Interval	Test(s)
Routine	At baseline and during follow-up	MRI/MRCP and endoscopic ultrasound Fasting blood glucose and/or HbA1c
Concerning abnormalities for which immediate surgery is not indicated	After 3 to 6 months	Repeat follow-up testing
No abnormalities or only non-concerning abnormalities (e.g., pancreatic cysts without worrisome features)	After 12 months	Repeat follow-up testing
If concerning features on imaging	Upon indication	Serum CA 19-9
Solid lesions of ≥5 mm Cystic lesions with worrisome features Asymptomatic main pancreatic duct strictures (with or without mass)	Upon indication	Endoscopic ultrasound-guided FNA
Solid lesions, regardless of size Asymptomatic main pancreatic duct strictures of unknown etiology (without mass)	Upon indication	CT
Positive FNA and/or a high suspicion of malignancy on imaging	Upon indication	Surgery[b]

[a]Age to initiate surveillance depends on gene mutation status and family history. There is no consensus on the age to end surveillance.

[b]When surgery is indicated, it should be oncologic radical resection at a specialty center.

CA 19-9 = carbohydrate antigen 19-9; CT = computed tomography; FNA = fine-needle aspiration; HbA1c = hemoglobin A1c; IPMN = intraductal papillary mucinous neoplasm; MRI/MRCP = magnetic resonance imaging/magnetic retrograde cholangiopancreatography = PanIN: pancreatic intraepithelial neoplasia.

Source: [70; 71] *Table 5*

As a relatively rare cancer, many primary care providers will only see a PDAC case every few years, making it imperative to elevate awareness of early PDAC signs and symptoms among these professionals. A retrospective case-control study in primary care found that patients sought medical attention 18 times on average in the period preceding their pancreatic cancer diagnosis. PDAC was associated with 11 alarm symptoms; back pain, lethargy, and new-onset diabetes were unique features of PDAC [75; 77].

Specific screening efforts in PDAC have focused on identifying high-risk individuals [48]. In 2020, the International Cancer of the Pancreas Screening (CAPS) Consortium updated its consensus recommendations for the management of individuals with increased risk of pancreatic cancer based on family history or germline mutation status [71]. For selected high-risk individuals, pancreatic surveillance is recommended to detect and resect early pancreatic cancer and its high-grade precursors (***Table 5***). No consensus was reached on whether surveillance should be performed for hereditary pancreatitis.

However, it is important to remember that among patients with PDAC unselected for their family history of pancreatic cancer who had a germline susceptibility gene mutation, only 10% of these patients had a family history of pancreatic cancer, and most did not have a cancer family history to suggest an inherited cancer syndrome. Because family history remains one of the best predictors of future pancreatic cancer risk, routine gene testing of patients with newly diagnosed PDAC and their families may yield significant clinical benefits [78].

Genetic counseling of patients before and after any genetic testing is essential, to provide understanding and reassurance and to avoid harm. A challenge to less restrictive testing of patients with new PDAC is there are not enough genetic counselors to provide this service; this shortage of expertise applies to other cancers as well [78].

GERMLINE AND SOMATIC TESTING AND MOLECULAR ANALYSIS

When should patients with pancreatic cancer have germline testing and gene profiling offered?

With strong consensus that benefits outweigh harms, in 2018 the ASCO recommended germline genetic testing for patients with PDAC, even if family history is unremarkable, if an informative result could directly benefit the patient or their family members [73]. This stance was adopted in 2020 by the NCCN. Consensus has subsequently expanded.

All patients with pancreatic cancer should have germline testing and gene profiling offered as quickly as possible after diagnosis; the implications for first-line therapy and beyond are significant [79; 80]. The 2020–2021 ASCO and NCCN recommendations are for all patients with PDAC to receive germline genomic testing using comprehensive gene panels for hereditary cancer syndromes, and targeted (somatic) profiling of tumor tissue using next-generation sequencing [10; 11]. Patients with locally advanced or metastatic PDAC should have available tumor tissue tested for DNA mismatch repair deficiency (dMMR) and microsatellite instability–high (MSI-H) status. It is also recommended that these patients undergo testing for actionable somatic mutations, including fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*), mutations (*BRAF*, *BRCA1/2*, *HER2*, *KRAS*, *PALB2*), and mismatch repair deficiency (dMMR).

CLINICAL EVALUATION OF PANCREATIC CANCER

Most pancreatic cancers (approximately 75%) originate in the head of the pancreas and typically metastasize to regional lymph nodes first, then to the liver. PDAC can also directly invade surrounding visceral organs (e.g., duodenum, stomach, colon); metastasize to any surface in the abdominal cavity via peritoneal spread where development of ascites carries an ominous prognosis; or spread to the skin as painful nodular metastases. By the time of diagnosis, 85% to 90% of patients have locally advanced tumors that have involved retroperitoneal structures, spread to regional lymph nodes, or metastasized to the liver or lung [2; 13; 24; 81].

Early-stage pancreatic cancer is notoriously difficult to diagnose. The most common symptoms in a series of patients diagnosed with PDAC were fatigue (86%), weight loss (85%), anorexia (83%), abdominal pain (79%), epigastric pain (71%), jaundice (56%), nausea (51%), diarrhea (44%), pruritus (32%), and steatorrhea (25%) [82].

Abdominal pain, jaundice, and weight loss are nonspecific, subtle in onset, and easily attributed to other processes. Unless the healthcare provider has a high index of suspicion for the possibility of underlying pancreatic carcinoma, this can make it difficult to know when to escalate a workup, as PDAC lacks a specified diagnostic algorithm [2; 24].

Development of abdominal pain, jaundice, or weight loss in the context of newly diagnosed diabetes, family history of PDAC, or history of pancreatitis should trigger inclusion of PDAC in the differential diagnosis [2]. Furthermore, past three-year onset of diabetes or ongoing hyperglycemia with significant weight loss and decreasing serum lipids should be considered a potential PDAC, even if abdominal pain or jaundice are absent, with urgent referral a priority.

As noted, pancreatic cancer-associated diabetes and pancreatic cancer cachexia are distinct paraneoplastic syndromes with clinical parameters that may alert attentive clinicians to pursue an appropriately aggressive workup [47]. The lethality of pancreatic cancer merits such an approach despite the absence of formal diagnostic guidelines in this area.

NEUROPSYCHIATRIC SYMPTOMS AND PANCREATIC CANCER

Depression is reported to be more common in patients with pancreatic cancer than with other abdominal tumors. In some patients, depression may be the most prominent presenting symptom, possibly secondary to delayed diagnosis. In addition, although patients may not communicate it to their families, they are often aware that a serious illness of some kind is occurring in them [24]. The risk of suicide among male patients with PDAC is almost 11 times higher than the general male population. Patients who underwent resection are more likely to commit suicide, specifically in the early postoperative period [83].

The association between mood disorders, fatigue, and PDAC has been assumed secondary to the psychosocial impact of diagnosis, loss of independence, and treatment toxicity [2]. However, it is now clear that PDAC has independent detrimental effects on the brain. These symptoms, often present before a diagnosis, are collectively the greatest drivers of declines in health-related quality of life and are independently predictive of survival. Evidence points to neuroinflammatory processes and the need to rethink PDAC as a systemic disease [2].

FAMILY HISTORY

The importance is emphasized of taking a thorough family history when seeing a new patient with pancreatic cancer. A family history of pancreatitis, melanoma, and pancreatic, colorectal, breast and ovarian cancers should be noted [11].

If a cancer syndrome is identified, at-risk relatives should be offered genetic counseling. With or without a known syndrome, individuals with a suspicious family history should be advised on risk-reducing strategies, including smoking cessation and weight loss. The possibility of screening for pancreatic and other cancers should be discussed.

Referral for genetic counseling should be considered for patients diagnosed with pancreatic cancer, especially those with a family history of cancer or who are young, those of Ashkenazi Jewish ancestry, or for whom a hereditary cancer syndrome is suspect. A free pancreatic cancer risk prediction tool, PancPRO, is available and may help determine risk [11].

COMMON PRESENTING SYMPTOMS AND SIGNS

Some, but not all, initial symptoms of PDAC result from a mass effect, such that pancreatic tumor location influences the stage of disease progression when symptoms appear [13].

Abdominal Pain

What are the most common signs/symptoms in patients with pancreatic cancer?

Abdominal pain is the most common symptom, usually insidious in onset and often present for one to two months at the time of presentation, the pain is often severe, and unrelenting in nature. The typical gnawing, visceral quality of pain is generally epigastric, radiating to the sides and/or straight through to the back; some patients may describe the pain as originating in the back. Nighttime pain is often the predominant complaint. Some patients note increased pain after eating and worsened pain when lying flat [24; 81]. Rarely, acute pain develops when an episode of acute pancreatitis results in tumor occlusion of the main pancreatic duct [84].

While roughly one-third of patients may not have pain at the time of initial presentation, all patients will develop pain at some point [24]. Pancreatic cancer is one of the most painful malignancies, and effective pain control is extremely important [85]. This issue will be discussed in detail later in this course.

Jaundice

The most characteristic sign of tumor in the pancreatic head is obstructive jaundice, for which patients may seek medical attention before their tumor grows large enough to cause abdominal pain (and thus, a somewhat better prognosis). These patients usually notice a darkening of their urine and/or lightening of their stools before they or their families notice the change in skin pigmentation. Jaundice secondary to a tumor in the body or tail of the pancreas typically occurs at a later stage and may be secondary to liver metastases of PDAC [2; 84].

Pruritus can accompany and often precedes obstructive jaundice. If present, it is often the patient's most distressing symptom [24].

Significant Weight Loss

A characteristic feature of pancreatic cancer, significant weight loss may be related to cancer-associated anorexia and/or subclinical malabsorption from pancreatic exocrine insufficiency caused by pancreatic duct obstruction. Nausea and early satiety from gastric outlet obstruction and delayed gastric emptying from the tumor can contribute to weight loss [24]. Significant weight loss is a symptom of cachexia.

Cachexia

Pancreatic cancer cachexia is a multifactorial paraneoplastic syndrome characterized by a loss of skeletal muscle mass, commonly associated with adipose tissue wasting and anorexia, fatigue, and reduced exercise tolerance. Cachexia develops in approximately 80% of patients with PDAC, in whom the syndrome is typically present at diagnosis and responds poorly to therapeutic interventions [47; 86].

Pancreatic cancer leads to the development of cachexia through a combination of distinct factors that explain its high prevalence and clinical importance in this disease [86]:

- Systemic factors, including metabolic changes and pathogenic signals related to PDAC tumor biology
- Factors resulting from the disruption of the digestive and endocrine functions of the pancreas
- Factors related to the close anatomic and functional connection of the pancreas with the gut

Additional Symptoms

The initial assessment can uncover additional diagnostic clues. Undiagnosed diabetes leads to symptoms of glucose intolerance (e.g., polyuria, polydipsia). PDAC can interfere with production of digestive enzymes by the pancreas (pancreatic exocrine insufficiency) and with the ability to break down food and absorb nutrients (malabsorption) in some patients. This malabsorption causes bloating, gas, and a watery, greasy, and/or foul-smelling diarrhea, leading to weight loss and vitamin deficiencies [81].

While long-standing diabetes is a risk factor for later development of PDAC, new-onset hyperglycemia or diabetes has been identified in the majority of patients at diagnosis of otherwise asymptomatic PDAC. Deregulation in glucose homeostasis is often accompanied by changes in subcutaneous adipose tissue. Both represent paraneoplastic syndromes caused by the underlying PDAC [2].

This research is among the most important knowledge advances in PDAC in the past decade. In addition to metabolic deregulation, the pre-diagnostic soft tissue changes and symptoms of cachexia have profound implications for screening, early diagnosis, treatment selection, and patient prognosis [2].

Tumors can also grow locally into the duodenum (proximal for the head of the pancreas, distal for the body and tail of the pancreas) and result in an upper gastroduodenal obstruction [13]. Tumor in the body or tail of the pancreas may cause splenic vein obstruction, resulting in splenomegaly, gastric and esophageal varices, and gastrointestinal hemorrhage [81].

PHYSICAL EXAMINATION

Clinical signs of PDAC during physical examination include jaundice, pruritus, steatorrhea, and vascular issues [2; 24; 82; 84]. Healthcare professionals can usually recognize clinical jaundice when total bilirubin reaches 2.5–3 mg/dL. Patients and their families do not usually notice clinical jaundice until total bilirubin reaches 6–8 mg/dL. Patients with jaundice may have a palpable gallbladder (i.e., Courvoisier sign). As noted, patients with clinical jaundice may have skin excoriations from unrelenting pruritus. If the pancreas has lost the ability to secrete fat-digesting enzymes or if the main pancreatic duct is blocked, steatorrhea will develop.

Migratory thrombophlebitis (i.e., Trousseau syndrome) and venous thrombosis may be present, reflecting the hypercoagulable state that frequently accompanies pancreatic cancer. Thromboembolic events (both venous and arterial) are especially prevalent in advanced disease, and thromboembolic complications occur more commonly with tumors in the pancreatic tail or body.

Multiple arterial emboli resulting from nonbacterial thrombotic endocarditis may be the presenting sign of PDAC. Marantic endocarditis (also known as nonbacterial thrombotic endocarditis) may develop in patients with pancreatic cancer and possibly mimic subacute bacterial endocarditis.

METASTATIC DISEASE

Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone [24; 84]. Patients presenting with or developing advanced intra-abdominal disease may have ascites, a palpable abdominal mass, hepatomegaly from liver metastases, or splenomegaly from portal vein obstruction. Subcutaneous metastases (termed Sister Mary Joseph nodules) in the paraumbilical area signify advanced disease; pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7% to 9% of cases [24; 84]. A metastatic mass in the rectal pouch may be palpable on rectal examination (Blumer shelf). As a metastatic node, left supraclavicular lymphadenopathy may be palpable, while other nodes in the cervical area may also be involved.

LABORATORY TESTING

Routine laboratory tests are often abnormal but nonspecific for PDAC. Common abnormalities include an elevated serum bilirubin and alkaline phosphatase levels, and presence of mild anemia [84].

Patients presenting with jaundice or epigastric pain should be evaluated with complete blood count, blood chemistry panel, and liver function tests to help assess the extent of cholestasis (bilirubin), liver metastasis (alkaline phosphatase), hepatitis (aminotransferases), and nutritional status (albumin, prealbumin). With epigastric pain, serum lipase should be measured to evaluate for acute pancreatitis [2].

DIFFERENTIAL DIAGNOSIS

Differential diagnosis before imaging and biopsy includes acute/chronic pancreatitis, cholangitis, cholecystitis, choledochal cyst, peptic ulcer disease, cholangiocarcinoma, and gastric cancer [85]. Unlike pancreatic exocrine tumors, the symptoms of pancreatic neuroendocrine tumors are distinctly related to excessive secretion of hormones such as insulin, glucagon, gastrin, somatostatin, and vasoactive peptide, resulting in hypoglycemia, hyperglycemia, and GI disturbances such as peptic ulcer and diarrhea.

THE DIAGNOSTIC AND STAGING WORKUP

It is not possible to reliably diagnose a patient with pancreatic cancer based on symptoms and signs alone. Abdominal imaging is used in the diagnostic and staging workup of a patient with suspected PDAC. Additional testing is based on the initial findings, the patient's clinical presentation and risk factors [2].

Accurate PDAC detection and staging at the time of presentation carries substantial implications for appropriate recommendation to patients of the most suitable treatment option, thus maximizing the survival benefit for patients in whom complete resection can be achieved and minimizing the morbidity from unnecessary laparotomy or major surgery in patients with high risk of residual disease following resection. The accuracy critically depends on the appropriate imaging protocol and radiologist experience [2; 87]. As such, decisions about diagnosis, resectability, and management of pancreatic cancer should involve multidisciplinary consultation at high-volume centers [11].

IMAGING

Multidetector Computed Tomography

What is the preferred imaging for initial evaluation of suspected PDAC?

Multidetector computed tomography (MDCT) angiography with intravenous (IV) contrast is the preferred imaging for initial evaluation of suspected PDAC. The Pancreatic CT Protocol standardizes its use, making MDCT highly accurate for assessing tumor extent, vascular invasion, and distant metastases [11; 16; 88; 89]. The NCCN recommends that MDCT angiography should also cover the chest and pelvis for complete staging [11].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Society of Clinical Oncology recommends a multiphase computed tomography (CT) scan of the abdomen and pelvis using a pancreatic protocol or magnetic resonance imaging (MRI) be performed for all patients with pancreatic cancer to assess the anatomic relationships of the primary tumor and to assess for the presence of intra-abdominal metastases.

(https://ascopubs.org/doi/10.1200/JCO.19.00946. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/high

MDCT is 77% accurate in predicting resectability and 93% accurate in predicting unresectability [85]. MDCT may be superior to magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) in vascular enhancement of a PDAC, the most important parameter of resectability. However, MDCT is inferior to MRI/MRCP in depicting isodense tumors or tumors smaller than 1.5 cm in size [54].

Magnetic Resonance Imaging/Magnetic Resonance Cholangiopancreatography (MRI/MRCP)

Abdominal MRI/MRCP with IV contrast also employs a standard multiphase protocol in PDAC, with efficacy comparable to MDCT in preoperative evaluation and assessment of vascular invasion. The sensitivity of MRI/MRCP in detecting liver metastases is nearly 100% (vs. 80% with MDCT) [81; 85].

Selection of initial MDCT or MRI/MRCP is typically based on local availability and expertise [81; 85]. Following initial MDCT, MRI/MRCP is used when PDAC is highly suspected but negative on MDCT, for characterizing small or indeterminate pancreatic and hepatic tumors, and in patients with severe allergy to iodinated IV contrast material used in MDCT [54; 81; 85].

Endoscopic Retrograde Cholangiopancreatography (ERCP)

With endoscopic retrograde cholangiopancreatography (ERCP), contrast dye is injected into the biliary ducts and pancreatic duct with an endoscope, and the level of obstruction is delineated. In some case, placement of a biliary stent can help relieve symptoms of jaundice [85]. Patients with obstructive jaundice may have ERCP as the first diagnostic procedure [81].

Ultrasonography

Transabdominal ultrasonography is useful in initial screening of patients who present with possible obstructive jaundice and can rapidly and accurately assess for biliary obstruction. However, definitive diagnosis requires other imaging [24].

Endoscopic ultrasonography is superior to MDCT in detecting solid pancreatic lesions less than 2 cm in size, with accuracy of about 92% [54]. Endoscopic ultrasonography-guided fine-needle aspiration (FNA) also allows for tissue sampling at the time of endoscopic ultrasonography diagnosis [24].

With the restricted field of view, endoscopic ultrasonography is complimentary to MDCT, but it should be used before other imaging options if no pancreatic mass is evident on MDCT. Endoscopic ultrasonography is also valuable in detecting tumor involvement of blood vessels or lymph nodes [11; 89].

Positron-Emission Tomography (PET)

Positron-emission tomography (PET) imaging alone does not offer added advantages to MDCT. Combining PET with CT (PET/CT) is a more recent development that may enhance the detection of occult metastases in pancreatic cancer. The NCCN guidelines consider PET/CT an evolving technology; its role in the diagnosis of PDAC is not yet established [11].

BIOPSY

A positive biopsy is not needed in patients with resectable PDAC before undergoing surgery; biopsy may result in seeding, interfere with definitive surgery, and needlessly delay surgical resection if nondiagnostic [11]. However, histologic confirmation of a pancreatic cancer diagnosis is required in some situations, and endoscopic ultrasonography-guided FNA biopsy is the best modality for obtaining a tissue diagnosis [84].

A pathologic diagnosis is indicated to confirm PDAC in locally advanced or metastatic disease, before neoadjuvant therapy, and in atypical presentations in which differential diagnosis is needed with other pancreatic masses (e.g., pancreatitis, lymphoma, tuberculosis). If a biopsy does not confirm malignancy, it should be repeated at least once [16].

The difficulty of diagnosing PDAC in patients with underlying chronic pancreatitis is noteworthy. In such cases, all typical imaging methods may show abnormalities that do not differentiate between PDAC and chronic pancreatitis, and carbohydrate antigen 19-9 (CA19-9) may be similarly elevated in pancreatitis. These patients may require combined multiple imaging modalities, close follow-up, serial imaging studies, and in some cases, empiric resection to diagnose an underlying pancreatic carcinoma [24].

CARBOHYDRATE ANTIGEN 19-9 (CA19-9)

CA19-9 is a sialylated Lewis A blood group antigen, commonly expressed and shed in benign and malignant pancreatic and biliary disease. Although unsuitable for asymptomatic screening, CA19-9 is the most clinically useful biomarker in PDAC, with good sensitivity (79% to 81%) and specificity (82% to 90%) in symptomatic patients. A normal serum level is 37 U/mL [90].

Preoperative CA19-9 provides important prognostic information. Levels <100 U/mL imply likely resectable disease, while levels >100 U/mL suggest unresectablity or metastatic disease. Fewer than 4% of patients with levels >300 U/mL have resectable tumors [24; 90].

In one study, patients with preoperative CA19-9 levels <37 U/mL showed longer median survival (22 to 40 months) than patients with levels >37 U/mL (7 to 30 months). Post-treatment changes (two to five weeks post-resection; six to eight weeks post-chemotherapy) from baseline may predict overall survival [90; 91].

Post-operative CA19-9 levels of <37 U/mL, <200 U/mL, and >500 U/mL were associated with three-year survival rates of 49%, 38%, and 0%, respectively. Post-chemotherapy CA19-9 decreases of ≥20% predicted prolonged disease-free survival and overall survival [90; 91].

Limitations

Around 5% to 10% of the population lacks the enzyme necessary to produce CA19-9; monitoring pancreatic cancer with this marker will not be possible in these individuals [24]. Biliary obstruction also stimulates the secretion of CA19-9. Hyperbilirubinemia is associated with elevated CA19-9 and false positivity in patients with obstructive jaundice. Following the treatment of obstruction, re-evaluation of CA19-9 should improve its diagnostic utility [92].

The NCCN recommends measurement of serum CA19-9 levels after neoadjuvant treatment, prior to and immediately following surgery before adjuvant therapy, and in surveillance. The importance is stressed of obtaining CA19-9 immediately before a therapeutic intervention to have an accurate baseline from which to follow response [11].

THE STAGING WORKUP

When a mass lesion of the pancreas is detected on MDCT (with or without additional imaging), it is reasonable to conclude that a neoplasm is present and is most likely malignant PDAC. After a probable diagnosis of pancreatic cancer is made, the next step is the staging evaluation to establish disease extent and resectability. Unlike many other cancers, imaging is the primary means through which the stage of pancreatic cancer is determined [11].

AMERICAN JOINT COMMISSION ON CANCER EXOCRINE PANCREATIC CANCER TNM STAGING	
Category	**Criteria**
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, including high-grade PanIN (PanIN-3) and IPMN, ITPN, or MCN with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
IPMN = intraductal papillary mucinous neoplasm; ITPN = intraductal tubulopapillary neoplasm; MCN = mucinous cystic neoplasm; PanIN = pancreatic intraepithelial neoplasia	
Source: [93]	*Table 6*

AMERICAN JOINT COMMISSION ON CANCER ANATOMIC STAGE/ PROGNOSTIC GROUPS FOR EXOCRINE PANCREATIC CANCER			
Stage	**T**	**N**	**M**
A	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–T3	N1	M0
III	Any T	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1
Source: [93]			*Table 7*

Using initial MDCT (with or without additional imaging), two different systems are involved [11; 93]:

- American Joint Committee on Cancer (AJCC) TNM staging system, to assess tumor status/extent (T), lymph nodes (N), and metastasis (M)
- NCCN guideline to characterize resectable, borderline resectable, or locally advanced disease

TNM Staging

The AJCC system (***Table 6***) is used for staging PDAC in two contexts [16; 94]:

- Clinical staging of all patients with imaging assessment of tumor size and extension, nodal involvement, and distant disease spread
- Pathologic staging of tissue specimens obtained during resection for presence of viable tumor cells

Clinical staging identifies the primary tumor and its vessel involvement, enlarged or suspicious lymph nodes, and metastatic disease sites. TNM staging provides important prognostic information (***Table 7***), but does not assess whether the PDAC tumor is amenable to surgical resection [54; 94].

Resectability Assessment

Complete resection is the only potentially curative treatment for PDAC, but fewer than 20% of patients presenting with PDAC have localized and easily resectable tumors, and noncurative resections provide no survival benefit. Thus, accurate assessment of resectability is crucial [24; 87; 89].

The NCCN guideline classes PDAC resectability into the following clinical stages [11]:

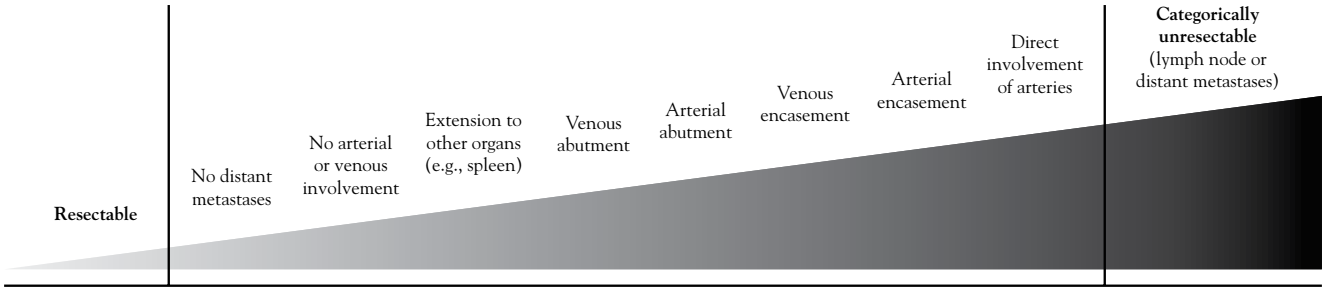
- Stage 1: Resectable
- Stage 2: Borderline resectable (i.e., tumors that are involved with nearby structures so as to be neither clearly resectable nor clearly unresectable with a high chance of removal of all macroscopic disease)
- Stage 3: Locally advanced (i.e., tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of metastatic disease)
- Stage 4: Metastatic (i.e., non-resectable)

Localized PDAC falls on a spectrum from high to low resectability, determined by the extent of vessel contact and whether the involvement is arterial or venous (***Figure 1***) [11; 54; 84; 87; 89; 95]. Major peripancreatic vessels include the superior mesenteric vein and artery, portal vein, common hepatic artery, and celiac artery. Tumor contact can be characterized as encasement (≥180 degrees of the vessel circumference), abutment (<180 degrees of the circumference), or direct involvement (absence of fat plane between tumor and vessel).

In the past, vascular infiltration by PDAC was considered unresectable, but surgical advances have increased the number of patients with initial borderline resectable or locally advanced disease who can undergo resection. In general, venous abutment or encasement is usually borderline resectable as long as the venous segment is reconstructable. Arterial reconstruction is substantially more difficult and risky than venous reconstruction with comparable tumor contact.

Based on PDAC clinical status of resectable, borderline resectable, locally advanced, or metastatic disease, additional considerations and therapeutic approaches will be undertaken. The time-urgency between the first availability of full imaging findings, multidisciplinary evaluation, the diagnostic and staging workup, discussion with the patient of available treatment options, and treatment initiation cannot be overstated in this aggressive malignancy.

SPECTRUM OF PANCREATIC CANCER RESECTABILITY



Source: [84; 89; 95] *Figure 1*

TREATMENT APPROACHES FOR PANCREATIC CANCER

As mentioned, the initial imaging workup of PDAC confirms the diagnosis, searches for evidence of metastases, and classifies nonmetastatic PDAC into resectable, borderline resectable, or locally advanced disease based on the involvement of surrounding arterial (superior mesenteric artery, common hepatic artery, and celiac axis) and venous (superior mesenteric vein or portal vein) structures, and other nearby organs and lymph nodes [96].

On average, 10% to 20% of patients initially present with "up-front" resectable PDAC. However, an increasing number of patients with initial borderline resectable or locally advanced disease are eligible for surgical resection as a result of neoadjuvant (i.e., before resection) therapies which may downstage the tumor, and advances in surgical technique, such as venous reconstruction in a vascular infiltration formerly considered unresectable [2].

In all therapeutic decisions, multidisciplinary collaboration to formulate treatment planning and disease management that incorporates patient preferences and available support, their comorbidity profile, symptom burden, and performance status should be the standard of care [6; 7; 10].

PATIENT FUNCTIONAL STATUS

Performance status is an important indicator of general well-being and the ability to perform activities of daily living in patients with cancer and is frequently assessed in both clinical and research settings. Performance status is repeatedly shown to predict important clinical outcomes, including quality of life, chemotherapy toxicity, response to chemotherapy, terminal illness, progression-free survival, and overall survival in patients with cancer [97].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the ASCO, the baseline performance status, symptom burden, and comorbidity profile of a person diagnosed with potentially curable pancreatic cancer should be carefully evaluated.

(https://ascopubs.org/doi/10.1200/JCO.19.00946. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/high

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE

Score	Definition
0	Fully active No performance restrictions
1	Strenuous physical activity restricted Fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities Up and about >50% of waking hours
3	Capable of only limited self-care Confined to bed or chair >50% of waking hours
4	Completely disabled Cannot carry out any self-care Totally confined to bed or chair
5	Deceased

Source: [98] *Table 8*

The Karnofsky Performance Status tool has been used for this purpose, but PDAC guidelines and randomized controlled trials now solely employ the Eastern Cooperative Oncology Group Performance Status (ECOG) scale (***Table 8***) [97]. For instance, some chemotherapies are indicated solely for patients with good ECOG performance status (0 or 1).

Baseline functional status and comorbidity profile should be carefully evaluated, because both have major implications for a person's ability to tolerate therapy. Performance status is consistently identified as a prognostic factor for people with pancreatic cancer. It is also an important determinant in treatment selection; some patients with up-front resectable PDAC may be physically weakened by weight loss and cachexia to an extent that places them at high risk of serious complications or mortality from definitive surgery. Performance status also helps predict chemotherapy toxicity, which can determine the treatment approach for patients with performance status 0 to 1 (multi-agent regimens) or performance status ≥2 (e.g., single-agent gemcitabine) [8].

Similarly, the comorbidity profile can influence the choice of chemotherapy, such as avoiding fluoropyrimidine-based regimens in patients with a known history of uncontrolled coronary artery disease. Nonetheless, performance status and comorbidities alone should not be used simply to rule in or out patients for treatment. For instance, disease control of comorbidities, such as controlled type 2 diabetes, can indicate that patient benefit from treatment may outweigh risks associated with poorly controlled comorbid diabetes [8].

RECOMMENDED TREATMENT OPTIONS BY CLINICAL STAGE

What is considered a curative treatment for PDAC?

Treatment approaches for PDAC include surgical resection, chemotherapy, radiation therapy, and combined regimens (chemoradiation therapy). Chemotherapy is the backbone of pancreatic cancer treatment; most patients present with disease too advanced to benefit from surgery or resection alone may be insufficient to provide a substantive survival advantage over best supportive care. Chemotherapy and radiation therapy also have a role in palliation, as will be discussed in a later section [99].

Curative surgical approaches for resectable pancreatic cancer are well-established. In contrast, the pace of new U.S. Food and Drug Administration (FDA) approvals and/or phase III evidence continue to make chemotherapy, molecular-targeted therapy, radiation, and chemoradiotherapy approaches a fluid, evolving area, requiring frequent updating and revisions in multidisciplinary clinical practice guidelines for pancreatic cancer treatment. Many potential treatment approaches lacking phase III or prospective evidence are being addressed, with publication of trial results awaited [2].

Resectable or Borderline Resectable PDAC

For patients with resectable or borderline resectable PDAC, neoadjuvant therapy consists of chemotherapy with or without radiation therapy before radical pancreatic resection [99]. Radical pancreatic resection may include Whipple procedure (pancreaticoduodenal resection) or total pancreatectomy when necessary for adequate margins. Distal pancreatectomy is indicated for tumors of the body and tail of the pancreas.

Following resection, patients may receive postoperative chemotherapy or postoperative chemoradiation therapy (typically fluorouracil [5-FU] chemotherapy and radiation therapy) [99].

Locally Advanced PDAC

Chemotherapy with or without targeted therapy is recommended for patients with locally advanced PDAC [99]. For patients without metastatic disease, this should be followed by chemoradiation therapy. If removal is a possibility, radical pancreatic resection may be attempted. Palliative surgery options include surgical biliary and/or gastric bypass, percutaneous radiologic biliary stent placement, or endoscopic biliary stent placement.

Metastatic or Recurrent PDAC

Treatment of metastatic or recurrent PDAC is limited to chemotherapy with or without targeted therapy [99]. Palliative approaches should be used whenever available and feasible to improve patient comfort and quality of life.

RESECTION OF PANCREATIC CANCER

Selecting patients for surgery should be based on the probability of cure as determined by resection margins. Other factors include comorbidities, overall performance status, and age. Pancreaticoduodenectomy and distal and total pancreatectomy are curative resection options based on the location, size, and locally invasive aspects of the tumor. Each has its own set of perioperative complications and risks, which should be considered by the surgical team and discussed with the patient [24].

Mortality rates from resection have fallen significantly, but morbidity remains common and interferes the delivery of adjuvant therapy in up to 40% of patients. The NCCN recommends that patients seek out high-volume centers performing more than 15 to 20 resections annually, with multidisciplinary expertise to optimize their treatment plan and increase opportunities for clinical trial participation [2].

The only curative treatment for PDAC is radical surgery, but potential cure is only possible with a microscopically negative resection margin (R0). Macroscopic (R2) and microscopic (R1) margin infiltration have survival trends similar to patients without surgery. R0 is a minimum >1 mm distance of viable tumor cells from the resection margin, R1 is ≤1 mm distance. A retrospective analysis of 44,852 patients with PDAC reported median survival of 19.7 months following R0, 14.3 months following R1, and 9.8 months with R2 resections compared with 10.3 months without surgery [100]. An incomplete tumor resection imposes morbidity risks without benefit to the patient, and the aim of resection is to obtain microscopically negative margins (R0) [101].

Tissue specimens obtained during resection are examined. During resection, lymphadenectomy is performed, including at least 15 lymph nodes, which are likewise examined as part of pathologic staging [16].

With surgical advances and greater use of adjuvant therapies, long-term cancer survival outcomes following resection were anticipated to improve over time [102]. However, in 1,147 pancreatic resections performed over three decades at the Memorial Sloan Kettering Cancer Center, a lack of progress in long-term survival was reported. Although patients treated between 2000 and 2009 had lower rates of operative mortality and greater one-year survival, for patients treated in the 1980s, 1990s, and 2000s, the median survival was 23.2, 25.6, and 24.5 months, respectively [103]. The five-year survival rates were 17%, 20%, and 8%, respectively. These data underscore the need for earlier detection and more effective systemic therapies [102].

Approaches

Pancreaticoduodenectomy (Whipple Procedure)

Used for tumors in the pancreatic head or periampullary region, the conventional Whipple procedure involves removal of the pancreatic head, duodenum, gallbladder, and the antrum of the stomach, with surgical drainage of the distal pancreatic duct and biliary system, usually through anastomosis to the jejunum. The primary reason for removing so much of the intra-abdominal structures is that they all share a common blood supply [24; 102].

The former high morbidity and mortality rates of Whipple have declined with the greater experience of a more limited number of surgeons who regularly perform the procedure in high-volume centers [102]. Common morbidities include delayed gastric emptying in roughly 25% of patients, which may require nasogastric decompression and a longer hospital stay. Pancreatic anastomotic leak can be treated with adequate drainage. Postoperative abscesses are not uncommon [24].

With operative mortality associated with Whipple decreasing from around 25% in the 1970s to less than 2% at high-volume centers in the 2010s, the focus has shifted from surviving the operation to surviving the cancer [104].

Distal Pancreatectomy

Distal pancreatectomy is a procedure for tumors in the pancreatic body or tail. It has a lower mortality than standard Whipple, but its use in curative resection is limited; with tumors in this location seldom causing bile duct obstruction, most patients present at a later stage with unresectable disease. The procedure involves resection of the distal pancreas containing the tumor with splenectomy and over-sewing of the distal pancreatic duct. Complications involve pancreatic stump leak, hemorrhage, and endocrine insufficiency. Laparoscopic exploration should precede attempted resection, because occult peritoneal metastases are common [16; 24].

Total Pancreatectomy

Total pancreatectomy, the least commonly performed procedure with the highest associated mortality (8.3%), may be needed to achieve an R0 resection margin for tumors in the neck of the pancreas, especially with extension into the body or tail, and in multifocal PDAC. Total pancreatectomy may be an option to pancreatic anastomosis in highly selected patients with a high-risk pancreas (small pancreatic duct) and obese patients with pancreatic fat infiltration. The metabolic consequences of permanent exocrine insufficiency and diabetes have a detrimental impact on quality of life and long-term survival [16; 24; 102].

Vascular Resection

Vascular involvement has traditionally been a formal contraindication to resection. With recent advances, venous resection and reconstruction can achieve R0 resection with similar overall survival and morbidity compared to surgery without venous resection. However, arterial resection during Whipple is associated with increased mortality and morbidity (bowel ischemia, hemorrhage, thrombosis) and is generally not recommended [16].

Progress in neoadjuvant therapies may downstage some tumors with arterial invasion to borderline resectable or resectable disease, making resection more achievable. Despite these advancements, it is currently accepted that arterial reconstruction is only appropriate in highly selected patients in high-volume centers with surgeons who are familiar with the advanced techniques required for reconstruction [16].

Total pancreatectomy should be considered in patients with locally advanced tumors who undergo pancreatectomy with arterial resection and reconstruction [16].

Biliary Drainage

In most patients with jaundice, early resection without biliary drainage is preferred. Preoperative drainage is indicated in patients with cholangitis or with obstructive jaundice scheduled for neoadjuvant therapy. Endoscopic retrograde placement of a fully covered metal stent is preferred. Endoscopic ultrasonography-guided stent placement is an effective and safe alternative [16].

CHEMOTHERAPIES IN PANCREATIC CANCER

As mentioned, the backbone of PDAC treatment is chemotherapy. Most patients present with advanced disease, and even those who undergo resection will require adjuvant chemotherapy. Chemotherapy is also used as neoadjuvant therapy and in metastatic disease with first-line or second-line indications [11].

Until recently, chemotherapies found effective in other GI cancers were applied to patients with advanced PDAC; the few agents showing any response became adjuvant therapies in localized PDAC. The near-futility in effective chemotherapy and redundancy in agents used in localized and metastatic PDAC reflects the pathologic complexity of this cancer and its profound resistance to cytotoxic therapies [2].

Since 2010, chemotherapy effectiveness has improved with the introduction of combination regimens, the identification of patients in whom mutational status conferred improved response to existing chemotherapies, and the introduction of novel compounds explicitly targeting mutational-related advanced PDAC.

CHEMOTHERAPY PROTOCOLS IN PANCREATIC CANCER			
Drug	**Dose and route**	**Administration**	**Given on days**
Gemcitabine Indication: Nonmetastatic PDAC Cycle length: 4 weeks (once weekly for 3 weeks, then 1 week off)			
Gemcitabine	1,000 mg/m^2 IV	Dilute in 250 mL NS (concentration ≤40 mg/mL), administered over 30 minutes.	Days 1, 8, and 15
Gemcitabine and capecitabine (GemCap) Indication: Adjuvant therapy Cycle length: 28 days Duration: 6 months			
Gemcitabine	1,000 mg/m^2 IV	Dilute in 250 mL NS (concentration ≤40 mg/mL), administered over 30 minutes.	Days 1, 8, and 15
Capecitabine[a]	830 mg/m^2 per dose oral	Twice daily (total 1,660 mg/m^2 per day), 12 hours apart. Swallow with water within 30 minutes post-meal.	Days 1 through 21
Modified FOLFIRINOX Cycle length: 14 days			
Oxaliplatin[b]	85 mg/m^2 IV	Dilute in 500 mL D5W, administer over 2 hours (before leucovorin). Shorter schedules (e.g., 1 mg/m^2 per minute) appear safe.	Day 1
Leucovorin	400 mg/m^2 IV	Dilute in 250 mL normal saline or D5W, administer over 2 hours (after oxaliplatin).	Day 1
Irinotecan[c]	150 mg/m^2 IV	Dilute in 500 mL normal saline or D5W, administer over 90 minutes concurrent with the last 90 mins of leucovorin infusion, in separate bags, using Y-line connection.	Day 1
Fluorouracil	2,400 mg/m^2 IV	Dilute in 500–1,000 mL 0.9% normal saline or D5W, administered as continuous IV infusion over 46 hours.[d]	Day 1
FOLFIRINOX Indication: Metastatic PDAC Cycle length: 14 days			
Oxaliplatin[b]	85 mg/m^2 IV	Dilute in 500 mL D5W, administer over 2 hours (before leucovorin). Shorter schedules (e.g., 1 mg/m^2 per minute) appear safe.	Day 1
Leucovorin	400 mg/m^2 IV	Dilute in 250 mL normal saline or D5W, administer over 2 hours (after oxaliplatin).	Day 1
Irinotecan[c]	150 mg/m^2 IV	Dilute in 500 mL normal saline or D5W, administer over 90 minutes concurrent with the last 90 mins of leucovorin infusion, in separate bags, using Y-line connection.	Day 1
Fluorouracil	400 mg/m^2 IV bolus	Give undiluted (50 mg/mL) as a slow IV push over 5 minutes (immediately after leucovorin).	Day 1
Fluorouracil	2400 mg/m^2 IV	Dilute in 500–1,000 mL 0.9% normal saline or D5W, administer as continuous IV infusion over 46 hours (immediately after IV bolus).[d]	Day 1

[a]Capecitabine is contraindicated in patients with known DPD deficiency.
[b]Many centers routinely infuse oxaliplatin via central venous line because of local pain with infusion into a peripheral vein
[c]Consider a lower dose of irinotecan with poor performance status.
[d]To accommodate an ambulatory pump for outpatients, can be administered undiluted (50 mg/mL) or the total dose diluted in 100–150 mL normal saline.

Source: [98; 105] *Table 9*

ACUTE AND DELAYED CHEMOTHERAPY TOXICITIES[a]		
Agent	**Acute Toxicities**	**Delayed Toxicities**
Fluorouracil	Nausea and vomiting Diarrhea	**Oral and GI ulcers** **Bone marrow depression** Diarrhea (especially with leucovorin) Neurologic defects, usually cerebellar Cardiac arrhythmias **Palmar-plantar erythrodysesthesia (hand-foot syndrome)**
Capecitabine	Nausea and vomiting	**Hand-foot syndrome** Diarrhea Stomatitis Dermatitis Bone marrow depression Hyperbilirubinemia
Gemcitabine	Fatigue Nausea and vomiting Fever	**Bone marrow depression** Edema Pulmonary toxicity
Irinotecan	**Diarrhea**	**Diarrhea** **Leukopenia**
Oxaliplatin	Peripheral sensory neuropathy Pharyngolaryngeal dysesthesias Paresthesias	Bone marrow depression Diarrhea Persistent neuropathy
Paclitaxel	Hypersensitivity reactions	**Bone marrow depression** Peripheral neuropathy Alopecia Arthralgias
[a]Dose-limiting toxicities are bold-faced.		
Source: [106; 107]		*Table 10*

FDA-Approved Chemotherapies in PDAC

Which chemotherapy agent/regimen has the strongest recommendation and level of evidence for use in patients with stage 3 (locally advanced) PDAC?

In addition to single chemotherapy agents, the FDA has approved regimens of these agents, including FOLFIRINOX (consisting of folinic acid [also referred to as leucovorin], fluorouracil [5-FU], irinotecan [IRN], and oxaliplatin [OX]) (***Table 9***) [3; 24; 80; 99]. Available chemotherapies are associated with acute and delayed toxicities, some of which can be dose-limiting (***Table 10***). ***Table 11*** summarizes the 2021 NCCN guideline for chemotherapy and chemoradiotherapy in PDAC.

According to the American Society of Clinical Oncology, all patients with resected pancreatic adenocarcinoma who did not receive preoperative therapy should be offered six months of adjuvant chemotherapy in the absence of medical or surgical contraindications. The mFOLFIRINOX regimen is preferred in the absence of concerns for toxicity or tolerance.

(https://ascopubs.org/doi/10.1200/JCO.19.00946. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/high

NCCN TREATMENT SUMMARY FOR PDAC		
Strength of Recommendation/ Evidence	**Regimen**	**Notes[a]**
Adjuvant stage 1 (resectable)		
Category 1	Gemcitabine Gemcitabine/capecitabine 5-FU/leucovorin	–
Category 2a	5-FU continuous infusion Chemoradiation	Chemoradiation should follow induction chemotherapy, with or without subsequent chemotherapy
Category 2B	Capecitabine	–
Neoadjuvant stage 1/2 (resectable or borderline resectable)		
Category 2A	Gemcitabine/paclitaxel NAB	–
Category 2B	Gemcitabine/cisplatin[b] FOLFIRINOX Chemoradiation	–
Stage 3 (locally advanced)		
Category 1	Gemcitabine	Preferred for patients with poor ECOG PS (≥2)
Category 2A	Gemcitabine/paclitaxel NAB Gemcitabine/erlotinib Gemcitabine/cisplatin[b] Gemcitabine/capecitabine Gemcitabine fixed-dose rate FOLFIRINOX Chemoradiation	Fixed-dose rate gemcitabine is a category 2B recommendation for patients with poor ECOG PS (≥2) Chemoradiation should follow induction chemotherapy, with or without subsequent chemotherapy
Category 2B	Gemcitabine/docetaxel/capecitabine Capecitabine 5-FU continuous infusion FOLFOX	–
Stage 4 (metastatic)		
Category 1	Gemcitabine Gemcitabine/paclitaxel NAB (preferred) Gemcitabine/erlotinib FOLFIRINOX (preferred)	–
Category 2A	Gemcitabine/cisplatin[b] Gemcitabine/capecitabine Gemcitabine fixed-dose rate Olaparib Pembrolizumab (for MSI-H or dMMR tumors only) Larotrectinib (for *NTRK*-positive only)	Fixed-dose rate gemcitabine is a category 2B recommendation for patients with poor ECOG PS (≥2) Olaparib for maintenance therapy only in *BRCA1/2* or *PALB2* mutated stage 4 disease without progression after 4 to 6 months of first-line platinum-based therapy
Category 2B	Gemcitabine/docetaxel/capecitabine Capecitabine[c] 5-FU continuous infusion[c] FOLFOX Entrectinib (for *NTRK*-positive only)	–

Table 11 continues to next page.

NCCN TREATMENT SUMMARY FOR PDAC *(Continued)*		
Strength of Recommendation/ Evidence	**Regimen**	**Notes[a]**
Second-line therapy		
Category 1	Gemcitabine[c,d] 5-FU/leucovorin/irinotecan[d]	–
Category 2A	Gemcitabine fixed-dose rate	Fixed-dose rate gemcitabine is a category 2B recommendation for patients with poor ECOG PS (≥2)
Category 2B	Capecitabine[c,e] 5-FU continuous infusion[c,e]	–
Strength of Recommendation Definitions		
Category	**Definition**	
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.	
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.	
[a]ECOG performance status (PS) 0/1 only, unless noted. [b]In *BRCA1/2* or *PALB2* mutations only. [c]Poor ECOG PS (≥2) only. [d]If prior non-gemcitabine-based therapy. [e]If prior gemcitabine-based therapy.		
Source: [11]		*Table 11*

Fluoropyrimidines

Fluorouracil is a fluorinated (fluoro)-pyrimidine antimetabolite that inhibits thymidylate synthase and interferes with RNA synthesis and function, with some effect on DNA.

Capecitabine is an oral fluoropyrimidine that undergoes hepatic hydrolysis to form fluorouracil. The final enzyme, thymidine phosphorylase, is present at higher levels in tumor tissue, providing better selectivity and tolerability.

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA polymerase and ribonucleotide reductase, which in turn inhibit DNA synthesis, blocks DNA replication and several forms of DNA repair [3; 24; 80; 99].

Erlotinib

Erlotinib is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. EGFR is expressed on the cell surface of normal cells and cancer cells. Erlotinib inhibits intracellular phosphorylation, which prevents further downstream signaling, resulting in cell death [3; 24; 80; 99].

Paclitaxel

Paclitaxel protein bound is a microtubular inhibitor (albumin-conjugated formulation) and a natural taxane that prevents depolymerization of cellular microtubules, which results in DNA, RNA, and protein synthesis inhibition [3; 24; 80; 99].

Irinotecan Liposomal

Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase-1 DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. Irinotecan liposomal is used in combination with fluorouracil and leucovorin [3; 24; 80; 99].

DNA Damage Repair Mutational Status and Targeted Therapies

Platinum agents (e.g., cisplatin, oxaliplatin) and olaparib are recommended in patients with mutation in DNA damage repair (DDR) genes by the NCCN. DDR mutations are present in up to 24% of PDACs, most commonly *BRCA1/2* and *PALB2*. Germline *BRCA1/2* mutations (gBRCAm)

affect approximately 7% of patients with PDAC [108]. DDR genes encode for proteins in the homologous repair pathway and DNA double-stranded break repair; thus, mutations may be more sensitive to further DNA damage [99].

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases; and disrupts DNA function. Oxaliplatin is an alkylating agent. Following intracellular hydrolysis, the compound binds to DNA, forming cross-links that inhibit DNA replication and transcription, resulting in cell death [24; 99].

PDACs with DDR mutations demonstrate improved responses to platinum-based therapies, and patients with advanced PDAC showed significantly improved median overall survival (22 months vs. 9 months) compared with nonplatinum therapy [96].

Poly (ADP-ribose) polymerase (PARP) inhibition has been posited to act synergistically with *BRCA1/2* mutations by inhibiting single-stranded break repair, causing an accumulation of DNA damage and tumor-cell death [99; 109]. Olaparib is a PARP inhibitor FDA-approved for PDAC with gBRCAm as maintenance therapy to sustain a progression-free state during platinum-based chemotherapy in metastatic PDAC [96].

The NCCN expands the use of olaparib to PDAC with gPALB2m. There are calls to expand these agents to PDACs with somatic DDR mutations [108].

Other FDA-Approved Targeted Therapies

The approved indications for the following agents are biomarker-defined, rather than by tumor site (e.g., pancreatic).

Pembrolizumab

Pembrolizumab is indicated in patients with microsatellite-instability-high (MSI-H) or dMMR mutations. Immune checkpoint inhibitors (ICIs) have efficacy in solid tumors with a high tumor mutational burden, and MSI-H or dMMR mutation solid tumors are associated with high tumor mutational burden. The ICI pembrolizumab is an anti-programmed death receptor-1 antibody that releases inhibition of the immune response, improving antitumor immunity [11; 96].

Pembrolizumab is approved for any solid tumor with MSI-H or dMMR mutation that progresses during treatment without any satisfactory alternative treatment options [11; 96]. This agent represented the first FDA approval (in 2017) with a biomarker-defined indication (i.e., agnostic of cancer site) [107]. Although this mutation is present in only about 1% of PDAC tumors, up to 83% of patients with dMMR PDAC respond to pembrolizumab [110].

ADJUVANT CHEMOTHERAPY TRIALS IN RESECTABLE PDAC

Phase III trial (Year)	Chemotherapy Comparison	Median Survival (months)
ESPAC-1 (2004)	5-FU vs. observation	21 vs. 15.5
CONKO-001 (2013)	Gemcitabine vs. observation	22.8 vs. 20.2
ESPAC-3 (2012)	Gemcitabine vs. 5-FU/leucovorin	46 vs. 39
ESPAC-4 (2017)	Gemcitabine/ capecitabine vs. gemcitabine alone	28 vs. 25.5
PRODIGE 24 (2018)	Modified FOLFIRINOX vs. gemcitabine	54.4 vs. 35
APACT (2019)	Gemcitabine/ paclitaxel vs. gemcitabine alone	40.5 vs. 36.2

5-FU = 5-fluorouracil.

Source: [2] *Table 12*

Larotrectinib and Entrectinib

Larotrectinib and Entrectinib are neurotrophin receptor kinase (NTRK) inhibitors approved (in 2018 and 2019) for advanced, morbid, or unresectable solid tumors with NTRK fusion mutations, found in less than 1% of PDCAs [96].

The mutation product, TRK fusion protein, activates mitogen activated protein kinase-extracellular regulated kinase and phosphoinositide3 kinase-serine threonine signaling pathways, implicated in the oncogenesis of pancreatic cancer [96]. The NCCN recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with NTRK gene fusion-positive locally advanced or metastatic PDAC [11].

Chemotherapy Efficacy: Localized Disease

A variety of data on chemotherapy efficacy are available, allowing for comparison of available agents in specific patient populations (***Table 12***). However, the terminology used can be confusing. Disease-free survival and progression-free survival are synonymous terms, and choice of the term used in this section will reflect the reference material. This is also the case with median survival and median overall survival. Unless noted otherwise, all patient outcomes are reported as median figures.

FIRST-LINE CHEMOTHERAPY TRIALS IN METASTATIC PDAC		
Phase III Trial (Year)	**Chemotherapy Comparison**	**Median Survival (Months)**
Cullinan (1985)	5-FU vs. 5-FU/doxorubicin vs. 5-FU/doxorubicin/mitomycin	5.5 vs. 5.5 vs. 4.5
Burris (1997)	5-FU vs. gemcitabine	4.4 vs. 5.6
Tempero (2003)	Gemcitabine vs. gemcitabine fixed dose rate	5 vs. 8
Heinemann (2006)	Gemcitabine ± cisplatin	6.0 vs. 7.5
NCIC-CTG PA.3 (2007)	Gemcitabine ± erlotinib	5.9 vs. 6.2
Cunningham (2009)	Gemcitabine ± capecitabine	6.2 vs. 7.1
CALGB 80303 (2010)	Gemcitabine ± bevacizumab	5.9 vs. 5.8
SWOG S0205 (2010)	Gemcitabine ± cetuximab	5.9 vs. 6.3
PRODIGE 4 (2011)	Gemcitabine vs. FOLFIRINOX	6.8 vs. 11.1
MPACT (2013)	Gemcitabine ± nab-paclitaxel	6.7 vs. 8.5
Source: [2]		*Table 13*

The CONKO-001 trial established gemcitabine as standard adjuvant chemotherapy. In this study, 354 patients were randomized to receive gemcitabine or observation after resection and followed a median 136 months. Gemcitabine led to a 24% improvement in overall survival, a 10.3% absolute improvement in 5-year survival (20.7% vs. 10.4%), and a 4.5% improvement in 10-year survival (12.2% vs. 7.7%), compared to observation [111; 112].

The ESPAC-3 trial showed the importance of completing the full post-resection adjuvant chemotherapy course (six cycles) in extending median overall survival of these patients compared with those not completing chemotherapy (28.0 months vs. 14.6 months) [96].

A continuation, ESPAC-4, found adding another fluoropyrimidine-based agent (capecitabine) to gemcitabine was superior to gemcitabine alone in median survival (28.0 months vs. 25.5 months) and five-year survival (28.8% vs 16.3%). A synergistic effect between gemcitabine and capecitabine on the DNA thymidylate enzyme was suggested [96].

PRODIGE-24 randomized 493 patients (ECOG performance status ≤1) with resected PDAC to modified FOLFIRINOX or gemcitabine for 24 weeks. At median 33.6 month follow-up, the disease-free survival with modified FOLFIRINOX was 21.6 months, compared with 12.8 months with gemcitabine [113]. Grade 3/4 toxicities were more frequent with mFOLFIRINOX (75.9%) than gemcitabine (52.9%). Nonetheless, the median 54.4-month overall survival with resection followed by mFOLFIRINOX is the longest survival reported to date with phase III results [5; 114].

Tolerance of adjuvant therapy remains a limitation, and patients commonly receive less than 50% of the planned dose, reflecting exposure to significant chemotherapy-related toxicity in patients experiencing substantial post-resection morbidity [2].

Chemotherapy Efficacy: Advanced/Metastatic Disease

First-Line Chemotherapy in Metastatic PDAC

5-FU has been used in pancreatic cancer treatment since the 1950s. Patients with advanced PDAC typically show response rates greater than 20% and median survival of 2.5 to 6 months [24; 80].

In 1997, gemcitabine replaced 5-FU as first-line treatment in metastatic PDAC by improving one-year survival rates (18% vs. 2%) and median overall survival (5.65 months vs. 4.41 months) [32]. Subsequently, numerous attempts to improve gemcitabine efficacy in metastatic PDAC have involved adding another cytotoxic drug [2; 96]. Some show marginal but statistically significant improvements in median survival over gemcitabine alone (***Table 13***).

The NCIC CTG PA.3 trial found a nonmeaningful clinical improvement with gemcitabine/erlotinib over gemcitabine alone in median overall survival (6.24 months vs. 5.91 months). Despite FDA approval for locally advanced/metastatic PDAC, the clinical impact of this modest gain with increased toxicity can be questioned [32; 96].

PRODIGE 4/ACCORD 11 demonstrated that patients with advanced PDAC and ECOG performance status ≤1 had better outcomes with FOLFIRINOX than gemcitabine in median overall survival (11.1 months vs. 6.8 months) and progression-free survival (6.4 months vs. 3.3 months). Following these findings, FOLFIRINOX became standard first-line therapy for candidate patients [2].

FOLFIRINOX was associated with more toxicities, but the six-month degradation in quality of life was better in FOLFIRINOX than gemcitabine (31% vs. 66%). Improved cancer control with FOLFIRINOX may be due to the inclusion of irinotecan, which has activity against PDAC and synergistic activity when given prior to 5-FU [96].

Finally, the MPACT study demonstrated an improvement of 1.8 months in both median overall survival and median progression-free survival with gemcitabine plus nab-paclitaxel versus gemcitabine alone, leading to another first-line option for metastatic PDAC [96].

Second-Line Chemotherapy in Metastatic PDAC

Second-line therapy primarily consists of doublet therapy using the alternative pyrimidine backbone to what was used in the first-line setting. In 2016, the NAPOLI-1 trial demonstrated that after progression on a first-line gemcitabine-containing regimen for metastatic PDAC, 5-FU/leucovorin plus nanoliposomal irinotecan improved overall survival from 4.2 months (with 5-FU/leucovorin alone) to 6.1 months. As with nab-paclitaxel, improving the delivery of traditional chemotherapies may lead to more effective treatments for individuals with pancreatic cancer [32].

The POLO trial examined targeted maintenance therapy in a biomarker-selected population. In patients with metastatic PDAC harboring germline *BRCA1/2* mutations who had not progressed on first-line platinum-based chemotherapy, those randomized to olaparib had improved median progression-free survival (7.4 months compared with 3.8 months with placebo), but olaparib did not improve median overall survival [109]. The median duration of response to olaparib was 6 months, but was more than 24 months in a subset of patients (23%), which is exceptional in metastatic PDAC [108].

In second-line chemotherapy after progression on a first-line regimen, there is considerable heterogeneity in the survival of patients, and predicting which patients will benefit is not established. The decision to pursue second-line chemotherapy should be individualized and based on the patient's goals and preferences. Factors influencing the choice of second-line therapy include the regimen used for first-line therapy, performance status and comorbidity, and mutation status [106].

RADIATION THERAPY FOR PANCREATIC CANCER

In addition to resection and chemotherapy, treatment of patients with PDAC may include radiation therapy or chemoradiotherapy. Unlike chemotherapy, the role of radiation therapy in the treatment of PDAC is uncertain. Radiation therapy is not a stand-alone treatment in local PDAC but is sequenced with chemotherapy as chemoradiotherapy.

Earlier adjuvant radiation therapy trials demonstrated an overall survival and disease-free survival benefit, but subsequent European chemoradiation studies showed negative findings [12]. Technical advances suggest increasing promise with radiation therapy, but multi-institutional randomized trials in PDAC have lagged [12].

Stereotactic body radiation therapy has promising local control and quality of life, and is being evaluated for locally advanced and borderline resectable PDAC. However, adjuvant stereotactic body radiation therapy remains investigational with high toxicity risk and is only recommended as part of a clinical trial [12].

In the absence of phase 3 trials directly comparing neoadjuvant treatment approaches with or without radiation, adjuvant and neoadjuvant chemoradiation in PDAC awaits definitive evidence. Several such trials are in progress [2; 12]. In particular, RTOG 0848 is expected to definitively clarify the role of post-resection radiotherapy [115].

Nonetheless, the prospective cohort and retrospective evidence suggestive of decreased local recurrence and disease progression is sufficient for ASTRO, the NCCN and ASCO to recommend radiation therapy. Standard radiation prescriptions in the neoadjuvant setting consist of daily treatments over the course of five or six weeks to a total dose of 50–54 gray (Gy) [2].

EVIDENCE-BASED PRACTICE RECOMMENDATION

Following surgical resection of pancreatic cancer, adjuvant conventionally fractionated radiotherapy with chemotherapy in select high-risk patients (i.e., positive lymph nodes and margins regardless of tumor location within the pancreas) is conditionally recommended by the American Society for Radiation Oncology.

(https://www.practicalradonc.org/cms/10.1016/j.prro.2019.06.016/attachment/0e8abbe7-fcc6-4c5d-8b46-e81e636ce080/mmc1.pdf. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Conditional/low

The type and duration of chemotherapy given with radiation therapy for pancreatic cancer depends on the clinical stage, setting (neoadjuvant or adjuvant), performance status, and comorbidities. Patients with favorable performance status (0 or 1) are typically offered FOLFIRINOX prior to radiation therapy. Patients who are elderly or have a poor performance status (≥2) are typically offered gemcitabine or gemcitabine/nab-paclitaxel prior to radiation therapy. The duration (two to six months or longer) depends on patient tolerance and tumor response (i.e., no evidence of progression on chemotherapy). Common dose-limiting toxicities are diarrhea, neuropathy, and hematologic [12].

NEOADJUVANT THERAPY

Preoperative, or neoadjuvant, therapy is a major paradigm shift in treatment for patients with localized PDAC that offers the potential to lengthen survival while sparing patients unnecessary treatment-related morbidity using available treatments [116]. The rationale for neoadjuvant therapy differs somewhat by disease stage and clinical features.

Neoadjuvant therapy is recommended in upfront resectable disease with high-risk features of dissemination. This includes tumors in pancreas body and tail or >3–4 cm, ascites, large regional lymph nodes, CA19-9 levels >1,000 U/mL, severe weight loss, and extreme pain. For these patients, staging laparoscopy is recommended to identify liver and peritoneal metastases missed by MDCT in assessing resectability, with endoscopic ultrasonography-guided biopsy [7; 11; 15]. The next step is systemic neoadjuvant therapy (i.e., chemotherapy), post-neoadjuvant therapy CA19-9, and MDCT with contrast to reassess resectability (with some limitations). If R0 resection is feasible and there is no evidence of metastatic disease, surgery should be attempted [7; 11; 15].

In general, neoadjuvant therapy for patients who are candidates for resection is controversial [116]. Some oncology groups do not recommend neoadjuvant therapy in upfront resectable disease (except with high-risk features) until better evidence is available, but this stance has become less tenable as additional evidence supporting efficacy becomes available [7; 13; 15].

Even in patients with anatomically localized disease based on imaging and after complete resection with R0 margins, the high rates of distant failure after surgery for resectable PDAC indicates most patients already have systemic disease at the time of diagnosis. Current imaging fails to accurately assess the true burden of disease, missing occult metastases and under-staging patients [116].

Given this reality, systemic therapy is crucial, but many patients do not receive adjuvant therapy after resection. The high complication rates and potentially prolonged recovery with resection results in 25% to 50% of patients not receiving postoperative therapy [116]. However, systemic neoadjuvant therapy allows patients to receive therapy when they have better performance status and before the potential development of postoperative complications [116].

Neoadjuvant therapy also tests the tumor biology. Patients with aggressive tumors that progress and/or metastasize during neoadjuvant therapy are spared a futile operation. Due to their performance status, patients who do poorly on systemic neoadjuvant therapy would likely do poorly with surgery, resulting in mortality or serious perioperative morbidity precluding adjuvant therapy. Neoadjuvant therapy allows patients with resectable tumors who are poor surgical candidates time to medically and/or physically optimize before surgery.

Neoadjuvant therapy is not without its drawbacks. Eligibility for neoadjuvant therapy requires a tissue diagnosis, but the dense PDAC tumor stroma impedes tissue confirmation in approximately 15% of patients [116]. Further, neoadjuvant therapy means delaying surgery, with the possibility for local progression during neoadjuvant therapy into unresectable PDAC [15]. However, local progression almost always occurs concomitantly with development of systemic disease [116]. Essentially, better evidence is needed. Until phase III results are available, the poor outcomes of conventional treatment sequencing argue for the need for neoadjuvant therapy.

Borderline resectable pancreatic cancer is a recognized indication for neoadjuvant therapy, as this approach may shrink and make tumors more amenable for surgical resection with fewer complications and increased chance of R0 resection. Neoadjuvant therapy may minimize early non-detectable microscopic metastases, decrease lymph node involvement, and improve overall survival and outcomes [96].

Upfront Resectable/Borderline Resectable Tumor and Neoadjuvant Therapy

What radiation dose is recommended for neoadjuvant chemoradiation?

The NCCN recommends neoadjuvant therapy for patients with resectable or borderline resectable tumors. Treatment at or coordinated through a high-volume center is preferred, when feasible, and participation in a clinical trial is encouraged. The preferred neoadjuvant options are FOLFIRINOX with or without subsequent chemoradiation, or gemcitabine plus albumin-bound paclitaxel with or without subsequent chemoradiation [11]. For patients with *BRCA/PALB2* mutations, the preferred regimen is gemcitabine plus cisplatin (two to six cycles) with or without subsequent chemoradiation [11].

ASTRO guidelines for neoadjuvant chemoradiation specify a radiation dose of 4,500–5,040 cGy in 180–200 cGy fractions [12]. They recommend delivery of radiation therapy following two to six months of chemotherapy.

Locally Advanced Pancreatic Cancer and Neoadjuvant Therapy

Locally advanced pancreatic cancer accounts for 30% of newly diagnosed cases. With local involvement of adjacent critical blood vessels and presence of occult micrometastatic disease, locally advanced pancreatic cancer is generally considered surgically unresectable and incurable, and the standard of care is similar to metastatic disease [2].

However, the increased use of preoperative multiagent chemotherapy followed by chemoradiation has significantly expanded the pool of patients with locally advanced pancreatic cancer eligible for resection with curative intent, significantly improving the resectability and overall survival of these patients [117].

In a single-institution phase II trial, 49 patients with locally advanced pancreatic cancer received eight cycles of FOLFIRINOX followed by 50.4 Gy of photon radiation with capecitabine and losartan. Of these patients, 39 were brought to the operating room, 34 (69%) had their cancer removed, and of these, 30 patients (88%) had an R0 resection. Among patients who underwent resection, median progression-free survival and overall survival were 21.3 and 33 months, respectively, versus the 11- to 12-month historical overall survival [118].

Neoadjuvant therapy is associated with a downstaging-to-resection rate of greater than 30% in selected patients with locally advanced pancreatic cancer, with survival comparable to or better than initially resectable disease. For patients with arterial involvement, arterial divestment shows a lower morbidity and mortality rate than arterial resection and reconstruction [117].

Post-Neoadjuvant Therapy Restaging Evaluation of Resectability

Following neoadjuvant therapy, a restaging evaluation with pancreatic protocol MDCT is required to image tumor shrinkage and rule out local progression for resectability. However, post-neoadjuvant therapy imaging is not a reliable indicator of resectability due to its inability to distinguish post-treatment fibrosis from residual viable tumor [117]. Post-neoadjuvant therapy CA19-9 levels are predictive of tumor regression and should be used to guide decisions about suitability for surgical exploration for resection. Diagnostic laparoscopy should be routinely used to minimize nontherapeutic surgery rates [117].

Adjuvant Chemotherapy in Patients with Resected PDAC After Neoadjuvant Therapy

After resection of pancreatic cancer following neoadjuvant FOLFIRINOX, the benefit of adjuvant chemotherapy on overall survival is unclear. Although randomized controlled trial confirmation is needed, a 2020 multicenter, retrospective study provided informative results [119]. Of 520 patients (median age: 61 years; 53.7% male) who received a median of six neoadjuvant cycles of FOLFIRINOX, 343 (66.0%) received adjuvant chemotherapy. Adjuvant chemotherapy was FOLFIRINOX for 68 patients (19.8%), gemcitabine-based chemotherapy for 201 (58.6%), capecitabine for 14 (4.1%), a combination or other agents for 45 (13.1%), and unknown for 15 patients (4.4%). The median overall survival was 38 months after diagnosis and 31 months after surgery. No survival difference was found for patients who received adjuvant chemotherapy compared with those who did not (29 months in both groups).

In multivariable analysis, the interaction of lymph node stage with adjuvant therapy was statistically significant. In patients with pathology-proven node-positive disease, adjuvant chemotherapy was associated with improved overall survival (26 months vs. 13 months). For those with node-negative disease, adjuvant chemotherapy was not associated with improved survival (38 months vs. 54 months). These results suggest that adjuvant chemotherapy after neoadjuvant therapy FOLFIRINOX and resection of pancreatic cancer was associated with improved survival only in patients with pathology-proven node-positive disease [119].

LOCALLY ADVANCED PANCREATIC CANCER

Neoadjuvant therapy increasingly shows the ability to downstage locally advanced pancreatic cancer into resectable tumor, but until such approaches are employed beyond specialized PDAC research centers, most of these patients will remain unresectable [2].

Chemotherapy selection for patients with locally advanced pancreatic cancer is largely based on extrapolation from studies in metastatic PDAC. However, the natural history of locally advanced pancreatic cancer is less predictable than metastatic disease [120]. In an important autopsy study, 28% of patients with locally advanced pancreatic cancer at initial diagnosis died with localized disease only, from complications of locally destructive tumor growth [120]. Also noted, not all isolated metastases at initial diagnosis are harbingers of widespread metastatic disease, nor the greatest threat to patient survival compared with the primary tumor or cachexia [17].

In patients with locally advanced pancreatic cancer, even with progression, treatment should not simply mirror that in metastatic disease. Rather, it should be based on the pattern of progression (locoregional vs. disseminated), prior chemotherapy and/or radiation, and sequence of therapy (as well as performance status and comorbidity). For example, if a patient with locally advanced pancreatic cancer and a history of only chemotherapy as prior treatment later develops locoregional progression, radiation may be the appropriate modality [8].

Fluoropyrimidines and gemcitabine are the most commonly used agents in adjuvant chemoradiotherapy trials of locally advanced pancreatic cancer. These studies suggest that as a radiosensitizer, capecitabine is a well-tolerated regimen with comparable or superior outcomes compared with low-dose gemcitabine [8].

There is a potential role for maintenance capecitabine or gemcitabine-based chemoradiotherapy in improving quality of life for patients with locally advanced pancreatic cancer and stable disease after 12 weeks of induction gemcitabine/capecitabine chemotherapy [8].

In contrast to conventionally fractionated chemoradiotherapy, there is growing interest in using induction chemotherapy for systemic control, followed by a short course of stereotactic body radiotherapy early during treatment with minimum disruption to systemic therapy. This could be particularly beneficial to patients with predominant local symptoms [8].

The ASCO guidelines for patients with locally advanced pancreatic cancer include several strong recommendations related to chemoradiotherapy or stereotactic body radiation therapy [2; 8]. Specifically, it states that chemoradiotherapy or stereotactic body radiation therapy may be offered upfront rather than chemotherapy [8]. This approach is recommended for patients with local progression but no metastases, performance status ≤2, and favorable comorbid profile. It should also be offered to patients with response to an initial six months of chemotherapy or with stable disease who develop chemotherapy toxicities that are intolerable or cause a decline in performance status [8]. If patients respond or their disease has at least stabilized after six months of induction chemotherapy, chemoradiotherapy or stereotactic body radiation therapy may be offered as an alternative to continuing chemotherapy alone [8].

For patients with unresectable or locally advanced pancreatic cancer, definitive conventionally fractionated or dose-escalated radiation therapy with chemotherapy is used. For patients without systemic progression after four to six months (or longer) of chemotherapy, ASTRO recommends definitive radiation therapy [12]. The preferred dose is 5,040–5,600 cGy in 175–220 cGy fractions.

Local Ablative Radiation

With surgical resection considered the only potentially curative option but most patients harboring unresectable PDAC tumor, nonoperative local treatment options that can provide a similar benefit are needed. Emerging radiation techniques that address organ motion have enabled curative radiation doses delivered in patients with inoperable disease [121].

In one 2021 report, patients with locally advanced pancreatic cancer were treated with hypofractionated ablative radiation therapy, using respiratory gating, soft tissue image guidance, and other methods to address organ motion and limit the dose to surrounding luminal organs [121]. At baseline, 119 patients with locally advanced pancreatic cancer and median CA19-9 level >167 U/mL received four months of induction chemotherapy, followed by ablative radiation therapy. The median overall survival from diagnosis and ablative radiation therapy were 26.8 and 18.4 months. The 12- and 24-month overall survival following therapy were 74% and 38%, and the 12- and 24-month cumulative incidence of locoregional failure were 17.6% and 32.8% [121]. Postinduction CA19-9 decline was associated with improved locoregional control and survival. Grade 3 upper GI bleeding occurred in 10 patients (8%), with no grade 4 to 5 events. This cohort study of patients with inoperable locally advanced pancreatic cancer found that ablative radiation therapy following multiagent induction therapy was associated with durable locoregional tumor control and favorable survival [121].

METASTATIC DISEASE

Systemic chemotherapy can benefit patients with metastatic PDAC by improving disease-related symptoms and survival compared with best supportive care alone, but patients should understand that chemotherapy is palliative and not curative [80].

First-line chemotherapy in metastatic PDAC is highly consistent in clinical practice guidelines from ASCO, NCCN and ESMO. Treatment selection is based on PDAC mutation status, serum total bilirubin level, ECOG performance status, comorbidity profile, patient preference and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services for FOLFIRINOX or mFOLFIRINOX.

The initial chemotherapy selection for germline or somatic *HRR* gene mutation is a platinum-based chemotherapy regimen. For those with performance status ≤1 and serum bilirubin less than 1.5 times upper limit of normal, FOLFIRINOX or mFOLFIRINOX is preferred. Gemcitabine plus cisplatin can be used and probably has similar benefit. For patients with performance status 2, comorbidity that precludes intensive therapy, or a serum bilirubin more than 1.5 times upper limit of normal despite stenting, FOLFOX is preferred over FOLFIRINOX.

After at least 16 weeks of initial platinum-based chemotherapy without disease progression, chemotherapy should be discontinued and maintenance therapy with olaparib initiated for those with germline *BRCA* or *PALB2* mutation. For advanced PDAC with somatic (i.e., non-germline) *BRCA* or *PALB2* mutation, the benefit of olaparib maintenance therapy is not known and is under investigation.

For patients with an unknown (pending) *HRR* status, waiting until the germline or somatic mutation status is known is not recommend, given the rapidity of progression in most patients with newly diagnosed metastatic PDAC. These patients should be treated like *HRR* mutation carriers until results of genetic testing are available [80].

Patients with performance status ≤1, serum bilirubin less than 1.5 times upper limit of normal, and favorable comorbidity, FOLFIRINOX is preferred, with gemcitabine plus nabpaclitaxel a potentially less toxic alternative. Patients with serum bilirubin more than 1.5 times upper limit of normal despite placement of a stent should receive FOLFOX rather than a gemcitabine-containing regimen, because gemcitabine is hepatically metabolized and associated with greater toxicity with hepatic impairment. For patients with performance status 2, favorable/adequate comorbidity, and serum bilirubin level less than 1.5 times upper limit of normal, gemcitabine monotherapy is suggested; gemcitabine/capecitabine is another option.

Highly selected patients with performance status 2 due to heavy tumor burden should be treated with gemcitabine plus nabpaclitaxel, owing to its higher response rate. Dose and schedule adjustments should be made to minimize toxicities. In patients with performance status ≥3 or poorly controlled comorbidity (regardless of histology or *BRCA*/*PALB2* mutation status), systemic chemotherapy should only be offered on an individualized, case-by-case basis; supportive care should be emphasized.

PALLIATION AND SYMPTOMATIC MANAGEMENT

At diagnosis, the median survival for patients with locally advanced, unresectable pancreatic cancer is 8 to 12 months; with metastatic disease, this decreases to 3 to 6 months. For patients with locally advanced and metastatic disease, systemic chemotherapy can improve survival. In the best outcomes to date, FOLFIRINOX demonstrated an 11.1-month median survival [122].

Patients receiving chemotherapy often report better overall quality of life, but extended survival with chemotherapy may not reduce symptom burden. Because the pancreas is located in the central abdomen at the root of the mesentery, most patients suffer from a significant symptom burden and frequently require medical attention and hospitalization for symptom management. Typical patients will require numerous interventions targeting pain, anorexia and weight loss, depression and anxiety, biliary obstruction, gastric outlet obstruction, ascites, and venous thromboembolism [122].

All patients with newly diagnosed PDAC should have a full assessment of symptom burden, psychological status, and social supports as early as possible. Regardless of cancer stage and patient prognosis, early introduction to expert palliative and supportive care improves the social, psychological, and physical well-being of patients; decreases the intensity of medical interventions at the end of life; and ultimately improves survival [2].

Palliative care is an interdisciplinary specialty that is focused on preventing and relieving suffering, and supporting the best possible quality of life for patients and their families facing serious illness, such as pancreatic cancer. Palliative care specialist clinicians provide in-depth pain and symptom management, communication regarding goals of care, and coordinated care across settings and over time. Palliative care aims to relieve suffering in all stages of disease and can be provided in tandem with curative or life-prolonging treatments [122].

When initiated early in the disease course, palliative care improves clinical, quality of care, and survival outcomes. Furthermore, multiple studies have shown that palliative care services improve patients' symptoms, allow patients to avoid hospitalization and to remain safely and adequately cared for at home, lead to better patient and family satisfaction, and significantly reduce prolonged grief and post-traumatic stress disorder among bereaved family members. Palliative care also lowers costs and reduces rates of unnecessary hospitalizations, diagnostic and treatment interventions, and nonbeneficial intensive care when patients are near the end of life [122].

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Pancreatic cancer is one of the highest-risk malignancies for venous thromboembolism (VTE), which includes deep venous thrombosis (DVT), pulmonary embolism, and visceral portal or superior mesenteric vein thrombi. The incidence of VTE is four- to seven-fold higher in PDAC. The risk is highest in the first three months after diagnosis; chemotherapy further increases the risk. In PDAC, VTE is strongly associated with higher short- and long-term mortality and high risk of recurrent VTE [122].

All patients should be educated about warning signs and symptoms of VTE. Physical examination of the legs for asymmetric pitting edema, erythema, and warmth is crucial in each office visit, and the threshold to perform a CT angiogram with tachycardia or pleuritic chest pain present should be extremely low [122].

Routine anticoagulation for primary VTE prevention is not indicated in ambulatory outpatients with pancreatic cancer and no other VTE risk factors [122]. In a patient with PDAC and documented VTE (symptomatic or incidentally found), early initiation of anticoagulation is the standard approach, and lifelong therapy should be considered. The decision to continue anticoagulation should be balanced against bleeding risk, cost of therapy, quality of life, life expectancy, and patient preference. Low-molecular-weight heparin or oral rivaroxaban, apixaban, or edoxaban is preferred to vitamin K antagonist or unfractionated heparin for long-term anticoagulation [122].

PERI-PANCREATIC COMPLICATIONS

Bile Duct Obstruction

Endoscopic retrograde stenting is superior to surgical or percutaneous approaches to address bile duct obstruction because of a more favorable adverse event rate. Self-expandable metal stents are preferred over plastic stents in patients with a life expectancy of more than three months in terms of patency duration, less therapeutic failure and need for reintervention, lower cholangitis incidence, and better patient quality of life. Patency rates between covered and uncovered metal stents are not significantly different [16]. Endoscopic ultrasonography-guided biliary drainage is an alternative if endoscopic biliary stent placement is unsuccessful or technically not feasible.

Gastric Outlet Obstruction

In patients with gastric outlet obstruction, endoscopic duodenal stenting allows a quick resumption of oral intake, with a low complication rate and a short recovery period. However, the need for reintervention is higher after duodenal stenting compared with that of palliative surgery. Endoscopic ultrasonography-guided gastrojejunostomy is an effective and safe alternative to surgery [16].

Ascites

Ascites in patients with metastatic PDAC may be due to peritoneal metastases. In patients with locally advanced tumors, ascites may be caused by portal vein thrombus if the tumor compresses the portal vein locally [122].

Patients with malignant ascites from pancreatic cancer can experience abdominal discomfort, nausea, vomiting, and dyspnea from the pressure of the fluid against the anterior abdominal wall and diaphragm. For most patients, survival is short, and the focus is symptom control. Symptom relief from intermittent paracentesis tends to be short-lived, and the procedure must be repeated for symptom relief. If reaccumulation requires more than once-weekly paracentesis, placement of a long-term drainage catheter is an option; complication rates are higher with indwelling catheters. Diuretics such as spironolactone and furosemide decrease the absorption of water and sodium in the kidneys and may provide some symptomatic relief [122].

PAIN CONTROL INTERVENTIONS

Pancreatic cancer is one of the most painful malignancies [85]. All patients with locally advanced and metastatic pancreatic cancer should be offered aggressive treatment of pain [8]. Adequate control of pain may be unsatisfactory due to significant variation in local practice [123].

Pain is often the major presenting symptom of the disease and can be a significant feature of advanced pancreatic cancer. Patients describe a gnawing mid-epigastric pain, which radiates bilaterally under the ribs and into the mid-back, owing to the proximity of pancreatic tumors to the celiac plexus. All patients should have the level of pain and degree of pain relief from analgesics addressed at every visit [122].

The ASCO recommends that patients with metastatic pancreatic cancer should be offered aggressive treatment of the pain and symptoms of the cancer and/or the cancer-directed therapy.

(https://ascopubs.org/doi/10.1200/JCO.20.01364. Last accessed August 19, 2021.)

Strength of Recommendation/Level of Evidence: Strong/intermediate

Pharmacotherapy

The mainstay of pain management is opioid therapy, and palliation of pain can often be successfully achieved by opioid analgesics alone [122]. Patients with moderate-to-severe pain should receive doses adequate to provide relief. Concern about addiction should not be a barrier to effective pain control; even with dose escalation, addiction is seldom a problem in patients with PDAC and the risk is lower than generally assumed in non-malignant pain [81; 123]. Given the ongoing concerns regarding opioid misuse in the United States, drug diversion may be a consideration. Accordingly, patients should be advised on safe storage strategies and disposal of any discontinued opioid or other controlled substance prescriptions to minimize diversion.

For patients with persistent nausea and vomiting for whom taking oral medications is difficult, pain control may be achieved using transdermal patches when adipose tissue is sufficient for transdermal absorption [122]. When pain is constant rather than intermittent, long-acting oral (e.g., morphine, oxycodone, oxymorphone) or transdermal (e.g., fentanyl, buprenorphine) preparations may work better [81]. Breakthrough pain can be treated with rapid-onset transmucosal or intranasal fentanyl formulations. Methadone may be advantageous in many patients and can be used in small doses as add-on to existing opioid treatment. Methadone should only by prescribed by clinicians who are familiar with the complex pharmacology and adverse effect profile of this opioid [123].

Laxatives should be considered for all patients on opioid analgesia for PDAC pain, because constipation is a nearly universal side effect. There is considerable individual variation in both efficacy and side effects. Not all patients benefit from or tolerate opioids. A trial of an alternative opioid may also be indicated. Cases of poor pain control or intolerable pain may benefit from continuous opioid infusion via epidural or intrathecal catheters [81; 123]. Adjunctive treatments, such as cannabinoids, ketamine, clonidine, benzodiazepines, anti-psychotics, gabapentin, pregabalin, nortriptyline, or duloxetine, warrant consideration [122].

Near the end of life, pain management for advanced and terminal PDAC can become very challenging, and an interdisciplinary approach including palliative care specialists is needed. It is important wherever possible to consider the preferences of the patient. A range of supportive care measures can be offered, including intensive home support, home care with parenteral opioids, patient-controlled analgesia, and palliative sedation [123].

Celiac plexus neurolysis offers medium-term relief, but other procedures (e.g., splanchnicectomy) are also available. Adjunctive treatments for pain, depression, and anxiety as well as radiotherapy, endoscopic therapy, and neuromodulation may be required. Palliative chemotherapy may provide pain relief as a collateral benefit [123].

Celiac Plexus Neurolysis

Neurolytic procedures reduce pain by destruction of the afferent pathways from the pancreas to the brain. One of the most commonly used procedures is celiac plexus neurolysis.

The celiac plexus is a dense network of nerves that innervates the upper abdominal organs. Pain may be relieved by inhibiting synaptic pathways within the plexus by chemical destruction of the pathways and ganglia using dehydrated alcohol. Celiac plexus neurolysis is performed under endoscopic ultrasonography guidance [122].

Celiac plexus neurolysis improves analgesia and quality of life and decreases opioid requirements. The analgesic effect seems to vanish after eight weeks, and in most patients, pain recurs after three months. Repeated celiac plexus neurolysis benefits about 30% of patients and is normally not offered [123].

Splanchnic Nerve Neurolysis

Splanchnicectomy may disrupt more nerve pathways than celiac plexus neurolysis and is a better option when there is a large mass in the region of the celiac plexus. Splanchnicectomy is seldom performed in patients with PDAC despite some evidence of long-lasting pain relief and few complications in observational series, possibly because the expertise is not widely available [123].

Radiation Therapy

External beam radiation therapy with or without concomitant chemotherapy may also significantly alleviate pain due to local invasion of pancreatic cancer, frequently with improvement in cachexia and obstructive symptoms. However, it may take several weeks to achieve its maximal effect. When pain is caused by liver or bone metastases, patients may benefit from radiation therapy [16; 122].

CACHEXIA, WEIGHT LOSS, AND NUTRITIONAL COMPROMISE

Nutritional compromise in PDAC is common, but the underlying pathologies are diverse [2]. Nausea, caused both by the primary disease process and its associated chemotherapy, is most effectively treated with serotonin-3 receptor antagonists and atypical antipsychotics (e.g., olanzapine), with some emerging evidence suggesting efficacy with cannabinoids. Loss of appetite, even in the absence of overt nausea, is frequently reported by patients, and this symptom is driven by central pathways that are largely distinct from those that produce nausea.

Malabsorption secondary to pancreatic exocrine deficiency degrades nutritional status. Pancreatic enzyme-replacement therapy helps to stabilize weight loss and also improves quality of life by decreasing gastrointestinal symptoms. Malabsorption from biliary obstruction is a complication found in up to 90% of patients with PDAC. Similar to the replacement of pancreatic enzymes, the treatment of biliary obstruction improves symptoms beyond its effects on digestion, including anorexia, pruritus, and fatigue.

Collectively, careful attention to the nutritional status of patients with PDAC improves both their survival and quality of life. Early and regular involvement of nutrition experts in their care is recommended [2; 124].

Cancer-Related Anorexia/Cachexia Syndrome (CACS)

A constellation of disproportionate loss of lean body mass, weight loss, muscle wasting, adipose tissue reprogramming, and anorexia, cancer-related anorexia/cachexia syndrome (CACS) is more frequent in patients with PDAC than in any other malignancy due to the complex metabolic profile of pancreatic cancer [2]. In a study of 390 patients with advanced cancers, the rate of cachexia was highest in PDAC (89%), followed by gastric cancer (76%) and esophageal cancer (53%) [125].

Unlike simple starvation, which is characterized by a caloric deficiency that can be reversed with appropriate feeding, the weight loss of cachexia cannot be adequately treated with aggressive feeding [126]. The physical impact of CACS contributes to decreased patient quality of life, treatment response, and survival due to gross alterations in protein metabolism, increased oxidative stress, and systemic

inflammation. The psychological impact also contributes to decreased quality of life for both patients and their families [125].

In CACS, an abnormally accelerated resting energy expenditure increases muscle protein breakdown and lipolysis, which seems related to activation of cytokines (e.g., tumor necrosis factor-alpha, interleukin 6 and 1 beta), and tumor-derived, potentially cachexia-inducing factors that target skeletal muscle gene products [122; 126].

Potentially Beneficial Agents

Which agents have proven efficacy in the treatment of anorexia associated with cancer-related anorexia/cachexia syndrome?

Cachexia in itself does not respond to nutritional support. There are no FDA-approved medications for treatment of CACS, and positive pharmacotherapy response in patients with anorexia associated with non-malignant disease has been difficult to translate into benefit for patients with cancer [127; 128].

Many agents have been evaluated for the treatment of CACS, but only corticosteroids (e.g., dexamethasone) and progesterone analogs (e.g., megestrol acetate) have a proven benefit in the anorexia associated with this syndrome [122]. Selection is based on life expectancy and assessment of risks versus benefits. Dexamethasone is suggested for patients for whom only weeks of therapy are anticipated, while megestrol acetate or medroxyprogesterone acetate (another progesterone analog) are suggested for patients with longer life expectancies [126].

A phase III study randomized 190 patients with advanced cancer and anorexia to megestrol acetate (480 mg/day), dexamethasone (4 mg/day), or placebo for up to four weeks. Differences in primary endpoint (at least 25% improvement in appetite) between megestrol (79.3%), dexamethasone (65.5%), and placebo (58.5%) were non-significant. Hyperglycemia and deep vein thromboses were more frequent with dexamethasone than megestrol or placebo. No other differences from placebo were found [127].

In this trial, the higher rate of deep vein thromboses with dexamethasone was unexpected. Megestrol acetate is associated with thromboembolic events and is contraindicated in patients with VTE. Dexamethasone has the potential to reduce cancer-related fatigue and elevate mood, at the significant cost of accelerating catabolic effects on muscle [127]. The primary benefits associated with these drugs are increased appetite and weight gain, not improved survival, and both drugs are associated with potential harms [122].

Mirtazapine is well-known for promoting weight gain. A placebo-controlled randomized trial found that appetite scores increased similarly with mirtazapine (15 mg at night) and placebo during the 28-day study. Mirtazapine was associated with significantly less increase in depressive symptoms and higher prevalence of somnolence than placebo, but no other differences were found [128].

The evidence of benefit in patients with CACS is inconclusive for androgens and selective androgen receptor modulators, anamorelin, cyproheptadine, long-chain omega-3 fatty acids, vitamins, minerals, and other dietary supplements, nonsteroidal anti-inflammatory drugs (NSAIDs), thalidomide, and combination approaches [126]. However, a trial of low-dose olanzapine (5 mg/day) is reasonable, particularly for patients who have concurrent nausea and/or vomiting unrelated to chemotherapy or radiation therapy [126].

Cannabis and Cannabinoids

In the cannabis plant, delta9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the best-characterized therapeutic constituents. Pharmaceutical cannabinoid products containing THC (dronabinol), a THC analog (nabilone), or THC:CBD in an oromucosal spray (nabiximols, investigational) were examined for efficacy in CACS and palliative care in two meta-analyses [126].

Unfortunately, no benefit beyond placebo was found for pharmaceutical cannabinoid products in CACS, despite their superior weight gain and appetite effects in patients with advanced HIV [129]. Cancer patients with more than 30% decrease in pain with cannabinoids compared with placebo approached significance [129].

In both meta-analyses, available studies of smoked cannabis in CACS did not meet evidence thresholds and were excluded. This limits the ability to inform real-world clinical practice, where patient preference, self-titration to tolerability/effect, access, and other factors favor smoked/vaped cannabis over single-molecule pharmaceutical cannabinoids [130].

Counseling and Support

The substantial loss of body mass can cause significant distress to patients. Although advanced cachexia is irreversible, palliating anorexia in patients with advanced cancer is best approached by focusing on stimulating appetite, supporting each person's food preferences, and avoiding prescriptive dietary advice [127].

Providing education to patients and their caregivers is crucial. The objective is to promote a shared understanding about changed goals of care, and to help reduce the distress caused by reduced oral intake [127].

Family members in particular can require educational intervention, as their distress may manifest in attempts to pressure or coerce the patient into increased feeding. Key points to discuss with patients and their family members, related to interactions about nutrition and eating near the end of life, include the following [131]:

- Loss of appetite is common in patients with advanced cancer and may be the result of the cancer process itself.
- Trying to force a patient to eat is usually counterproductive, potentially leading to increased nausea/vomiting.
- In most patients with advanced cancer and cachexia, providing additional calories by feeding tubes and/or intravenously does not improve outcomes.
- Trying to make a patient eat, when they have marked appetite loss, can lead to decreased social interactions and increased patient distress regarding interactions with caregivers (including stories of patients, in their dying days, pretending to be asleep when relatives visit, so that the relatives do not try to make them eat something).

Caregivers should be advised that it may be best to listen to and support the patient in a variety of other ways (such as giving the patient a massage or applying a lip moisturizer) instead of trying to talk them into eating more. Referral to a registered dietitian may provide patients and caregivers with additional opportunities to discuss concerns and challenges related to nutrition, appetite, and meal planning.

Diabetes Mellitus in PDAC

The presence of diabetes has been associated with higher mortality in patients with PDAC; corticosteroids can induce or exacerbate diabetes in these patients. For patients with PDAC-related diabetes, nutritional management by an experienced dietitian is essential [16]. Metformin or insulin is used as a first-line therapy. Insulin is often the preferred agent because of its efficacy, flexibility, and safety.

Careful monitoring of plasma glucose levels two hours after meals is widely recommended. The limited literature on this topic recommends maintaining blood glucose levels to avoid hypoglycemia and reduce symptoms of hyperglycemia.

Pancreatic Exocrine Insufficiency and Pancreatic Enzyme Replacement Therapy (PERT)

A contributory factor to extreme weight loss may be pancreatic exocrine insufficiency, which leads to maldigestion, fat malabsorption, and steatorrhea. The main clinical manifestation is weight loss and malnutrition, and nonspecific symptoms such as abdominal cramping, flatulence, and urgency to defecate. Fat malabsorption does not become evident until pancreatic lipase secretion falls below 10% of normal levels [122].

Pancreatic exocrine insufficiency results from loss of pancreatic parenchyma and/or tumor obstruction of the main pancreatic duct, and can occur after surgery or irradiation. The characteristic fatty stools associated with steatorrhea (loose, greasy, foul-smelling) may not be evident because patients tend to limit fat ingestion [122].

Pancreatic exocrine insufficiency is very frequent (>90% with tumors in the pancreatic head), and is associated with higher mortality in patients with unresectable PDAC. Pancreatic enzyme replacement therapy (PERT) improves survival in these patients [16]. Given its high incidence, diagnostic testing is not necessary. Patients suspected of fat malabsorption should be treated empirically with oral PERT [122].

The classical approach to patients with pancreatic exocrine insufficiency was restricting fat intake (<20 gm/day) in an attempt to reduce steatorrhea. However, this further restricts the intake of fat-soluble vitamins, which are already malabsorbed in patients with pancreatic exocrine insufficiency, and is not recommended. Frequent low-volume meals and avoidance of foods that are difficult to digest (e.g., legumes) are generally recommended [122].

Pancreatic exocrine insufficiency is treated with capsules of porcine pancreatic enzymes (pancrelipase). There are a number of commercial products available, and the amount of enzyme per capsule varies [81]. Doses are in United States Pharmacopeia (USP) units or International Units (IU); 90,000 USP is equivalent to 30,000 IU [122]. A healthy pancreas produces about 900,000 USP of lipase in response to a meal. Sufficient fat absorption can be maintained at around 10% of normal capacity; thus, roughly 90,000 USP per meal is needed. Because non-resected patients retain some pancreatic function, a starting dose of 75,000 USP with main meals and 25,000 with snacks should suffice in reducing steatorrhea and preventing weight loss. Enzymes are most effective when taken across the course of a meal. Following Whipple, patients will require 90,000 USP with meals and 45,000 USP with snacks [124].

Acidic gastric pH is normally neutralized by pancreatic bicarbonate secretion, which is absent in many patients with PDAC, especially following Whipple resection. Acid-suppressing therapy with a proton pump inhibitor is often required, as failure to neutralize gastric acid inactivates the enzymes [16; 124].

Despite recommendation from expert groups, including the NCCN, evidence suggests PERT is underutilized. This was examined in a large commercially insured U.S. population from 2001–2013. Among patients with PDAC (32,461), 1.9% had diagnostic testing for exocrine insufficiency, 21.9% filled a prescription for PERT, and 5.5% were prescribed an adequate dose (defined as ≥120,000 USP lipase daily) [132].

Testing and appropriate dosing is infrequent and inconsistent in an insured U.S. population. Efforts are needed to educate medical providers on the best practices for managing exocrine pancreatic insufficiency in these patients [132].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding all aspects of their care (including diagnostic procedures and treatment options) and palliative care resources be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter. In any case in which information regarding treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered. Print materials are also available in many languages, and these should be offered whenever necessary.

CONCLUSION

PDAC is the most lethal solid malignancy, predicted to become the second leading cause of cancer death in the United States by 2030. The complexity of this aggressive cancer has been vexing to investigators and tragic for patients and their families. Major research efforts over the past 50 years have only marginally improved the five-year survival rate from 6% to 10.8%. The greatest gains—from resection of early-stage tumors—are the least likely to present at diagnosis. There is an urgent need to reduce PDAC incidence through primary and secondary prevention, and mortality by accelerating therapeutic development [133].

Until diagnostic or therapeutics breakthroughs arrive, novel uses of standard treatments (i.e., neoadjuvant therapy) show survival advantages for a greater number of patients. The longest survival reported by a phase III trial was published in 2018—a median 54.4 months in patients who received resection followed by mFOLFIRINOX [113]. Many novel treatments are in phase III trials. Additional approaches to manage morbidities and provide better palliative care are also needed. Cancer anorexia/cachexia is a high-priority area.

It is now clear that even early-stage PDAC is a systemic disease and that new-onset metabolic (e.g., diabetes, anorexia/cachexia, hyperglycemia) and neuropsychiatric (e.g., depression, fatigue) symptoms/syndromes are prodromal rather than comorbid or secondary. This recognition has also called for a re-thinking of pancreatic cancer from a more integrative, multi-system perspective [2].

Customer Information/Evaluation insert located between pages 44–45.

Men's Health Issues

Includes 5 Pharmacotherapeutic/Pharmacology Hours

Audience

This course is designed for nurses, physicians, physician assistants, and behavioral health professionals seeking to enhance their knowledge of issues related to men's health.

Course Objective

The purpose of this course is to provide health and mental healthcare professionals with necessary information regarding conditions and health issues that affect men in order to facilitate more effective diagnosis, treatment, and care. As male-specific factors influence the provision and compliance to therapy, tools to ensure effective patient education for men are provided to increase the likelihood of positive outcomes.

Learning Objectives

Upon completion of this course, you should be able to:

1. Identify diseases that are more prevalent among men than among women.
2. Describe the health implications of male gender identity and identify strategies to improve communication with male patients.
3. Explain the diagnosis and treatment of benign prostate conditions and prostate cancer.
4. Apply guideline recommendations for prostate cancer screening.
5. Describe treatment options and assist patients in selecting a management strategy for localized prostate cancer.
6. Distinguish among benign testicular conditions.
7. Discuss the diagnosis and treatment options for testicular cancer.
8. Discuss the differences between male and female breast cancer.
9. Discuss diagnosis and treatment options, and assist patients in selecting a treatment strategy for sexual dysfunction (premature ejaculation and erectile dysfunction).
10. Devise a strategy for diagnostic testing and treatment of late-onset hypogonadism.
11. List factors affecting male infertility.
12. Promote patient education and disease prevention, implement effective screening, and select guideline-appropriate treatment of sexually transmitted infections.
13. Identify issues of particular concern for men who have sex with men.
14. Discuss the effects of substance misuse, depression, and stress/anger on the physical and psychosocial well-being of men.
15. Discuss the importance of educating men about the need for screening, routine health maintenance, and healthy lifestyle.

Faculty

Lori L. Alexander, MTPW, ELS, MWC, is President of Editorial Rx, Inc., which provides medical writing and editing services on a wide variety of clinical topics and in a range of media. A medical writer and editor for more than 30 years, Ms. Alexander has written for both professional and lay audiences, with a focus on continuing education materials, medical meeting coverage, and educational resources for patients. She is the Editor Emeritus of the *American Medical Writers Association (AMWA) Journal*, the peer-review journal representing the largest association of medical communicators in the United States. Ms. Alexander earned a Master's degree in technical and professional writing, with a concentration in medical writing, at Northeastern University, Boston. She has also earned certification as a life sciences editor and as a medical writer.

John M. Leonard, MD, Professor of Medicine Emeritus, Vanderbilt University School of Medicine, completed his post-graduate clinical training at the Yale and Vanderbilt University Medical Centers before joining the Vanderbilt faculty in 1974. He is a clinician-educator and for many years served as director of residency training and student educational programs for the Vanderbilt University Department of Medicine. Over a career span of 40 years, Dr. Leonard conducted an active practice of general internal medicine and an inpatient consulting practice of infectious diseases.

Faculty Disclosure

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Contributing faculty, John M. Leonard, MD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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NetCE designates this continuing education activity for 18 hours for Alabama nurses.

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This course represents an educational model that promotes the importance of learning objectives and individualized learning. Study questions will appear throughout the course to create a link between the learning objectives and the supporting text.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the study questions and course material for better application to your daily practice.

INTRODUCTION

There are many reasons to be concerned about health issues that are unique to or more common in men. In 1900, women outlived men by an average of two years; that gap widened to seven years in 1970 through 1990 [1]. Advances in diagnosis and treatment, as well as heightened awareness of disparities in men's and women's health, led to a narrowing of the gap to slightly less than five years in 2014 [1]. Still of concern, however, is the high number of men's deaths that are potentially avoidable. Many factors contribute to the disparity in mortality and morbidity between men and women, but the factor thought to have the most significant impact on the health of men relates to male gender identity, including a tendency for risky behavior [2; 3; 4; 5].

The concept of men's health was established to focus on the high rates of morbidity and mortality. Thus, men's health encompasses both male-specific conditions, such as those related to the prostate, as well as diseases that affect men at a higher rate compared with women. A discussion of all diseases that affect men is beyond the scope of this course. However, the leading causes of death among men are presented and discussed in the context of how they compare with the causes of death in women.

Among the male-specific conditions addressed are prostate disease (e.g., prostatitis, benign prostatic hypertrophy [BPH], cancer), testicular conditions (e.g., testicular torsion, epididymitis, varicocele, cancer), premature ejaculation, erectile dysfunction, late-onset hypogonadism, infertility, and sexually transmitted infections (STIs). Prostate cancer is discussed in considerable detail. Prostate screening and treatment have been controversial issues in health care, and the most recent recommendations for how to discuss screening and treatment options are included. Also provided are brief overviews of male breast cancer, a rare disease but one that is rising in prevalence, and health issues of specific concern for men who have sex with men (MSM), a growing population seen in the primary care setting.

The psychosocial well-being of men is integral to overall health. The link between anger and stress and disease is mentioned, as is the major role of substance misuse in mortality and morbidity. Alcohol misuse and depression have both been underdiagnosed in men, especially older men, and strategies for screening are explored.

The course closes with suggestions for fostering enhanced healthy behaviors among men, with recommendations for reaching out to men, ensuring appropriate health screening, and encouraging healthy behaviors.

OVERVIEW OF MEN'S HEALTH ISSUES

The concept of men's health emerged in response to the documented trends in greater mortality rates for men compared with women. Over the past decade, attention to the causes of death and disease in men has increased, and a growing body of scientific literature has begun to elucidate gender differences in physiologic, psychologic, and sociologic aspects of disease. These differences have a strong influence on the health of men as well as on the response to treatment and health behaviors.

Men's health lacks the same type of clinical focus as women's health; that is, men's health does not have the equivalent of a specialist (gynecologist) to provide care for the reproductive tract. Care of the male reproductive tract is assumed by primary care physicians, urologists, endocrinologists, reproductive specialists, and possibly, oncologists. The discipline of andrology is in its early stages, and some have proposed that this discipline should be expanded beyond the reproductive tract to include all men's health issues, with a goal of developing appropriate training programs and establishing a distinct specialty [6]. Men's health programs at large academic centers as well as free-standing centers in large cities are providing multidisciplinary diagnostic and management services targeted to men.

As defined by most organizations around the world, the field of men's health encompasses a broad range of health issues, including diseases that are more prevalent among men than women or that differ with regard to risk factors, diagnosis, and treatment. Men's health also addresses the psychologic and social influences on men and acknowledges the need to model healthier attitudes beginning in boyhood.

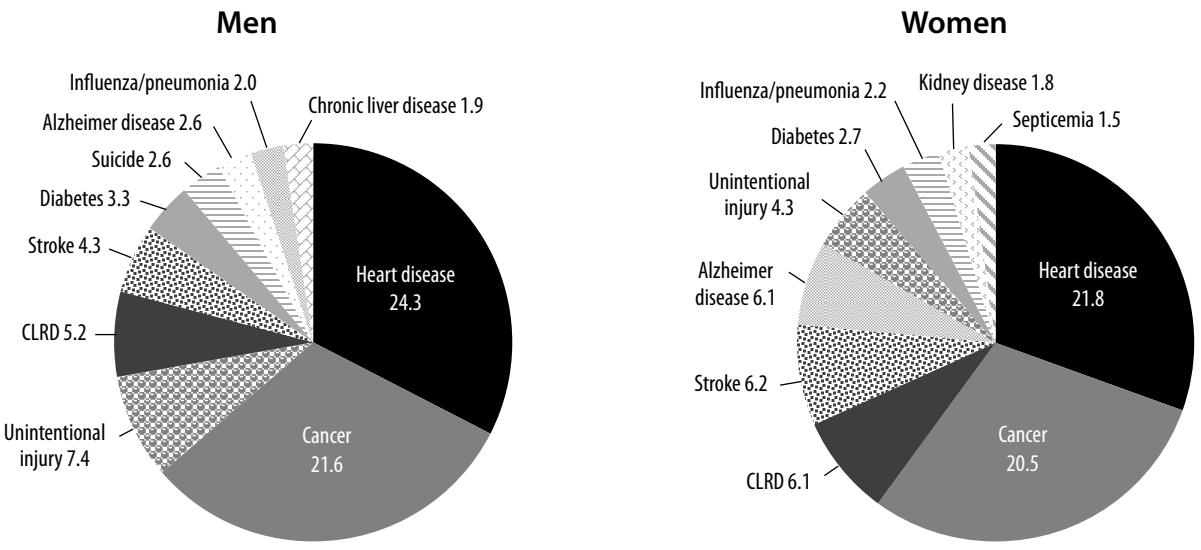
Several initiatives have helped to promote awareness of men's health among the public, policy arena, and scientific community, including establishment of the Men's Health Network, a nonprofit organization based in Washington, DC, and targeted peer-review journals such as the *Journal of Men's Health* and the *American Journal of Men's Health*.

MORBIDITY AND MORTALITY AMONG MEN

Which causes of death are more prevalent among men than women?

In general, the leading causes of death among men and women are the same; what differs are the age at the time of death, the number of deaths caused by each disease, and the ranking of the causes (***Figure 1***) [7; 8]. The overall death rate in 2019 was higher for male than female individuals (all ages) (846.7 vs. 602.7 per 100,000) [9; 10]. Cardiovascular disease and cancer are the two leading causes of death for both men and women, but a greater percentage of men die of each cause [9; 10]. Deaths related to cardiovascular disease and cancer account for approximately 46% of the total number of deaths among all men [7]. In 2019, the death

THE LEADING CAUSES OF DEATH AMONG MEN AND WOMEN, 2018



CLRD = Chronic lower respiratory disease.

Source: [7; 8] *Figure 1*

TEN LEADING CAUSES OF DEATH FOR MEN ACCORDING TO RACE/ETHNICITY, 2018

Leading Causes of Death	Mortality Rate and Rank					
	All Men	White	Black/ African American	Hispanic/ Latino	Asian/Pacific Islander	American Indian/ Alaskan Native
Cardiovascular diseases	24.4% (1)	24.8% (1)	24.1% (1)	20.2% (1)	23.1% (2)	18.9% (1)
Cancer	22.2% (2)	22.2% (2)	19.7% (2)	19.4% (2)	24.7% (1)	15.9% (2)
Unintentional injuries	6.8% (3)	6.9% (3)	—	11.3% (3)	5.3% (4)	13.7% (3)
Chronic lower respiratory diseases	5.3% (4)	5.8% (4)	3.2% (7)	3.3% (6)	3.2% (6)	3.6% (7)
Stroke	4.2% (5)	4.1% (5)	5.0% (4)	4.7% (4)	6.7% (3)	2.9% (8)
Diabetes mellitus	3.1% (6)	2.9% (6)	4.4% (6)	4.2% (5)	4.2% (5)	5.7% (5)
Suicide	2.5% (7)	2.7% (8)	—	3.1% (8)	2.6% (8)	4.2% (6)
Alzheimer disease	2.5% (8)	2.9% (7)	7.9% (3)	2.3% (9)	2.3% (9)	—
Influenza and pneumonia	2.0% (9)	2.0% (9)	1.7% (10)	3.2% (7)	3.2% (7)	2.2% (10)
Chronic liver disease	1.9% (10)	1.7% (10)	—	4.1% (6)	—	6.1% (4)
Assault (homicide)	—	—	4.5% (5)	2.2% (10)	—	2.3% (9)
Kidney disease	—	—	2.7% (8)	—	2.0% (10)	—
Septicemia	—	—	1.7% (9)	—	—	—

Source: [11] *Table 1*

COMPARISON FOR LIFETIME RISK FOR CANCERS FOR MEN AND WOMEN

Cancer Type	Lifetime Risk	
	Men	Women
All sites	40.2%	38.5%
Lung and bronchus	6.4%	6.0%
Colon and rectum	4.2%	4.0%
Melanoma of the skin	3.7%	2.5%
Non-Hodgkin lymphoma	2.4%	1.9%
Kidney and renal pelvis	2.2%	1.3%
Leukemia	1.9%	1.3%

Source: [16] *Table 2*

TEN LEADING CANCER TYPES FOR THE ESTIMATED NEW CANCER CASES AND DEATHS BY SEX, UNITED STATES, 2022

Estimated New Cases

	Males			Females	
Prostate	268,490	27%		Breast	287,850	31%
Lung & bronchus	117,910	12%		Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%		Colon & rectum	70,340	8%
Urinary bladder	61,700	6%		Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%		Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%		Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%		Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%		Pancreas	29,240	3%
Leukemia	35,810	4%		Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%		Leukemia	24,840	3%
All Sites	**983,160**	**100%**		**All Sites**	**934,870**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	68,820	21%		Lung & bronchus	61,360	21%
Prostate	34,500	11%		Breast	43,250	15%
Colon & rectum	28,400	9%		Colon & rectum	24,180	8%
Pancreas	25,970	8%		Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%		Ovary	12,810	4%
Leukemia	14,020	4%		Uterine corpus	12,550	4%
Esophagus	13,250	4%		Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%		Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%		Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%		Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**		**All Sites**	**287,270**	**100%**

Source: Reprinted with permission of Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. *Figure 2*

rate from Alzheimer disease was 30% lower among men than women; the death rates from cerebrovascular diseases, influenza/pneumonia, and chronic lower respiratory diseases were approximately the same for each biologic sex [7; 8]. The causes of death differ within the male population according to age and race/ethnicity, highlighting disparities related to socioeconomic status, cultural differences, access to care, and possibly, genetic predisposition for specific diseases (***Table 1***) [11].

Review of the leading causes of death demonstrates that many men's deaths are potentially avoidable. Most notable is the third leading cause of death for all men: unintentional injuries [11]. Unintentional injuries cause substantially more deaths among men than women, for whom it is the sixth leading cause of death [12]. Suicide is the eighth leading cause of death among all men; this cause of death is not included in the top 10 causes for women. In addition, homicide is among the ten leading causes of death for Black, Hispanic/Latino, and American Indian/Alaska Native men [13; 14; 15]. Several of the other leading causes of death among men are associated with chronic diseases, for which modification of risk factors and early detection can improve outcomes.

Gender differences exist in the prevalence of specific cancers and in deaths related to cancers [16]. The lifetime probability of being diagnosed with invasive cancer is higher for men than women (***Table 2***) [16]. The rate of deaths associated with cancer of the colon/rectum, urinary bladder, esophagus, and liver and intrahepatic bile duct are higher among men than among women (***Figure 2***) [16]. Although prostate cancer is the most prevalent cancer in men and receives widespread attention, lung cancer is responsible for a greater percentage of cancer-related deaths among men (23% vs. 11%) [16].

MALE GENDER IDENTITY AND IMPLICATIONS FOR HEALTH

An increasing amount of research is supporting a relationship between men's risk for disease and death and male gender identity, and the traditional male role has been shown to conflict with the fostering of healthy behaviors [4; 17]. Male gender identity is related to a tendency to take risks, and the predilection for risky behavior begins in boyhood [17; 18; 19]. In addition, boys are taught that they should be self-reliant and independent and should control their emotions, and societal norms for both boys and men dictate that they maintain a strong image by denying pain and weakness [4; 18; 19].

Issues related to male gender identity have several important implications for health. First, risky behavior is associated with increased morbidity and mortality. Second, the concept of masculinity leads to inadequate help- and information-seeking behavior and a reduced likelihood to engage in behavior to promote health [4; 18; 19]. These behaviors appear to be rooted in a decreased likelihood for men to perceive themselves as being ill or at risk for illness, injury, or death [4]. Third, male gender identity, coupled with lower rates of health literacy, creates special challenges for effectively communicating health messages to men [5; 20; 21]. Gender differences in health-related behaviors are consistent across racial/ethnic populations, although specific behaviors vary according to race/ethnicity [17].

Risky Behavior

Risky behavior affects health and well-being beginning at a young age. The overall rate of fatal injuries is approximately two times higher among boys than girls (0 to 19 years of age) [22]. Motor vehicle accidents are the leading cause of death for both genders, especially in the age category of teenage drivers (15 to 19 years of age). Although not all of these injuries and deaths are related to risky behavior, Youth Risk Behavior Surveillance (YRBS) data indicate that many of them are related; other risky behaviors identified in this survey are related to morbidity and mortality in adolescence and are also contributors to habits that affect health in adulthood. The 2019 YRBS showed that the rate of risky behaviors is predominantly higher among male respondents (***Table 3***) [23]. The rates of many of these behaviors continued to be higher among male adults (***Table 4***), which plays a role in premature deaths among men [1; 24].

Men's predilection for risky behavior is reflected in the high rate of unintentional injury, which accounts for 7.4% of deaths among men (compared with 4.3% for women) [7; 8]. There is wide variation in this rate across race/ethnicity, with much higher rates among American Indian/Alaska Native men (13.7%) and Hispanic/Latino men (11.3%) [11]. The trend of more fatal unintentional injuries among men is evident in countries around the world; an analysis of accidental deaths among men and women in 36 countries showed higher rates for men [2]. Across all age-groups, the rates were higher in the United States than the median rate for all countries. Accidental deaths are related primarily to motor vehicle injuries, violence, and occupation, and the rates in all categories are higher for men than for women. The rate of death related to motor vehicle injuries for men is slightly higher than for women (16.0 vs. 6.3 per 100,000), and the percentage of fatal unintentional firearm-related injuries deaths occur overwhelmingly more often among men (82.7%) than women (17.3%) [25]. Similarly, fatal occupational injuries occur predominantly in men (57% vs. 6%) [26].

Substance misuse plays a significant role in both risky behavior and the development of chronic diseases. As demonstrated by the YRBS data, the use of tobacco, alcohol, and illicit drugs begins in the teenage years, with more boys than girls engaging in such behavior [23]. One exception appears to be prescription opioids, which are more likely to be misused by female adolescents than male adolescents. Among adults, substance misuse continues to be more prevalent among men than women [27]. Misuse of tobacco, alcohol, and drugs are associated with high rates of unintentional injuries, violence, STIs, and masking of depression [25; 28; 29; 30].

COMPARISON OF RISKY BEHAVIORS IN YOUTH (9th THROUGH 12th GRADES)		
Behavior	**Male Respondents**	**Female Respondents**
Did not always wear a seat belt	43.3%	42.7%
Rode with a driver who had been drinking alcohol	15.6%	17.5%
Texted or e-mailed while driving	39.6%	38.4%
Drove after drinking alcohol	7.0%	3.6%
Carried a weapon (gun, knife, or club)	19.5%	6.7%
Was in a physical fight in the previous 12 months	28.3%	15.3%
Currently smoke cigarettes daily	6.9%	4.9%
Currently use smokeless tobacco	5.8%	1.6%
Currently use electronic vapor product (e-cigarettes, e-cigars, e-pipes, vape pipes, vaping pens, e-hookahs, hookah pens)	32.0%	33.5%
Had >5 drinks of alcohol within a couple of hours on >1 of the previous 30 days	12.7%	14.6%
Ever used marijuana	37.0%	36.5%
Drove after using marijuana	14.6%	11.3%
Ever misused prescription opioids	12.4%	16.1%
Ever used cocaine	4.9%	2.7%
Ever used heroin	2.3%	1.0%
Ever used methamphetamines	2.7%	2.7%
Source: [23]		*Table 3*

RISKY BEHAVIOR AMONG ADULTS		
Behaviors[a]	**Men**	**Women**
Non-seat belt use	11.6%	7.2%
"Heavy" drinking (five or more drinks on the same occasion on at least five days of the last month)	8.2%	4.0%
Five drinks or more in a day at least one day within the previous month	28.5%	20.7%
Current smoking	15.6%	12.0%
Use of illicit drugs[a]		
Any illicit drug (past month)	14.0%	9.5%
Cannabis (past month)	12.3%	8.0%
Psychotherapeutic drug (nonmedical use in past month)	2.1%	1.9%
[a]Data for behaviors are based on individuals 18 years of age and older; the data on use of illicit drugs are based on individuals who were 12 years of age and older.		
Source: [1; 24]		*Table 4*

The rate of tobacco use among men has declined over the past decade, but the rate continues to be higher than that among women [31]. The Centers for Disease Control and Prevention (CDC) estimates that men who smoke increase their risk of death from lung cancer by 25 times, with tobacco being the cause of approximately 90% of all lung cancer deaths in men [32]. In addition, smoking is a significant risk factor for many cancers, especially those that are more prevalent among men, and is linked to a two to four times greater likelihood of cardiovascular disease or stroke [32].

Excessive alcohol use is the third leading lifestyle-related cause of death for both men and women, and long-term use of alcohol is a well-recognized contributor to several chronic diseases [33]. Even consumption that is considered to be less than "hazardous" (three to five drinks per day) has been associated with increased morbidity and mortality [34].

Help- and Information-Seeking Behavior

How does male gender identity affect men's health?

Help- and information-seeking behavior related to male gender identity is another factor that affects men's health. In general, men are reluctant to seek health care or talk about their health because they see such help-seeking as a sign of weakness or vulnerability and a threat to their masculinity [4; 35; 36]. These reports are substantiated by data on utilization of healthcare resources, which indicate that men have fewer office visits to doctors or other health care professional than women; in 2018, 23.9% of men had no office visits, compared with 12.5% of women [37]. In addition, men are more likely to lack a usual source of health care (18.6% vs. 10.7%) [37]. Men have reported several reasons for not having a usual source of care, and the reasons vary among racial/ethnic populations [39]. The reason given most often is that they are seldom or never sick, and this may be related to men's perceptions of invulnerability [39; 40]. Other reasons given include not finding time and not being able to take time away from work [38]. Cultural values, such as *machismo*, lead many Hispanic men to avoid health care until there is no other choice [40]. This may contribute to the low rate of healthcare use among Hispanic men, which is the lowest across racial/ethnic populations [40]. Other reasons for the low use of healthcare services among Hispanic men are lack of health insurance, low understanding of the healthcare system, fear of poor functional outcomes, and a low perception of the quality of the patient-clinician interaction [40]. In the Black population, men have reported to avoid healthcare services because of fears and concerns about their negative health behaviors and history [41].

Lower rates of healthcare use among men have a negative impact on preventive care, and rates of routine health assessments and recommended vaccinations and screening procedures have been lower among men than among women [42]. Several factors contribute to the avoidance of screening tests, including men's belief that they are healthy; their focus on their present, rather than future, health; the need for more information about the screening procedure; and other issues related to masculinity [42]. For example, Black men have reported avoiding screening for prostate and colorectal cancer because they see these procedures as "violating their manhood" [41; 43].

Among men who do have physician office visits, many are not forthcoming about symptoms or information they seek [44]. Because of their traditional discomfort with expressing feelings and emotions, they are less likely to seek help for psychosocial problems or emotional symptoms [17; 45]. Men tend to be more motivated to seek health care for male-oriented conditions, such as erectile dysfunction or sports-related injuries, or when their health or symptoms interfere with their routine activities [45].

Communicating Effectively with Men

Effective communication is essential in the healthcare setting but can be challenged by several factors. Specific challenges in communicating with men are related to male gender identity as well as to low health literacy and language and cultural barriers.

Male Gender Identity

Men's beliefs about masculinity and traditional male roles affect health communication, and healthcare practitioners should consider male-specific beliefs and perceptions when communicating with male patients. For example, because men tend to focus on present rather than future health, concepts of fear, wellness, and longevity often do not work well in health messages [40]. Instead, healthcare practitioners should focus more on "masculine" concepts, such as strength, safety, and performance, all of which tie into men's perceptions of their roles as providers and protectors. To address men's reluctance to admit pain, practitioners should avoid asking questions such as "Do you have pain?" and instead use phrases such as "Most men I see with this condition say they have quite a bit of pain—what about you?" Using numbers/statistics and metaphors relating the body to a machine may also help to communicate effectively by addressing male gender identity. In addition, practitioners should be nonjudgmental about their male patients' health and risk behaviors and develop open lines of communication to encourage them to express their health concerns.

Health Literacy, Language, and Culture

According to the National Assessment of Health Literacy, 14% of individuals in the United States have "below basic" health literacy, which means they lack the ability to understand health information and make informed health decisions [21; 46]. The findings of the assessment demonstrated that the rate of "below basic" literacy was higher among men than women (16% vs. 12%) [21]. Although the rate of "basic" health literacy was similar for men and women, rates of "intermediate" and "proficient" health literacy were lower for men [21]. Similar rates of health literacy have been found in subsequent studies, with rates of adequate health

literacy consistently lower among men and even lower among non-White men [47; 48]. In one study, the rate of adequate health literacy was 48% among White men (compared with 63% among White women) and 23% among non-White men (compared with 30% among non-White women) [48].

Recognition of the importance of adequate health literacy to good health outcomes has led to assessment of health literacy being deemed "the newest vital sign," with development of an assessment tool by that name [48; 49]. The Newest Vital Sign (NVS) tool has been shown to demonstrate the health literacy status in fewer than three minutes, with results that are comparable to those of more extensive literacy tests [48]. Clinicians are encouraged to use this tool to assess the literacy of their patients, especially those of racial/ethnic minorities, and to adapt discussions to literacy levels and provide low-literacy educational resources. Compounding health literacy are language and cultural barriers, which have the potential for far-reaching effects, given the growing percentages of racial/ethnic populations. According to U.S. Census Bureau data from 2020, 21.5% of the American population speak a language other than English, and of those, 8.2% speak English less than "very well" [50]. Clinicians should ask their patients what language they prefer for their medical care information, as some individuals prefer their native language even though they have said they can understand and discuss symptoms in English [51]. Translation services should be provided for patients who do not understand the clinician's language. "Ad hoc" interpreters (family members, friends, bilingual staff members) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, clinicians should check with their state's health officials about the use of ad hoc interpreters, as several states have laws about who can interpret medical information for a patient [52]. Even when allowed by law, the use of a patient's family member or friend as an interpreter should be avoided, as the patient may not be as forthcoming with information and the family member or friend may not remain objective [52]. Children should especially be avoided as interpreters, as their understanding of medical language is limited and they may filter information to protect their parents or other adult family members [52]. Individuals with limited English language skills have actually indicated a preference for professional interpreters rather than family members [53].

Most important, perhaps, is the fact that clinical consequences are more likely with ad hoc interpreters than with professional interpreters [54]. A systematic review of the literature showed that the use of professional interpreters facilitates a broader understanding and leads to better clinical care than the use of ad hoc interpreters, and many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care and that the use of professional interpreters improves communication (errors and comprehension), utilization, clinical outcomes, and patient satisfaction with care [55; 56]. Clinicians should use plain language in their discussions with their patients who have low literacy or limited English proficiency. They should ask them to repeat pertinent information in their own words to confirm understanding, and reinforcement with the use of low-literacy or translated educational materials may be helpful.

MALE-SPECIFIC DISORDERS

Among male-specific disorders, prostatic conditions are perhaps of most concern to men and have raised the most questions in the healthcare community about diagnosis, screening, and treatment. Sexual health issues, such as premature ejaculation and erectile dysfunction, are also of substantial concern to men, and treatments for these conditions gained increased attention beginning in the late 1990s. The prevalence of many STIs is on the rise, especially among younger men, posing a significant public health problem [57]. Infertility is an issue for many younger men, and interest in late-onset hypogonadism has increased, primarily because of the debate about the use of testosterone replacement therapy. Much attention has also been focused on the unique healthcare needs of a minority population—MSM. (This term has become preferred as a more accurate description because of the variation in how such men identify themselves sexually [58].) Another minority population is that of men with breast cancer, a disease that has become more prevalent since the 1980s. The diseases and conditions noted here by no means represent all of those related to the health care of men. Topics were chosen on the basis of their impact on the overall health of men and the implications for care.

Primary care and family medicine physicians and other general healthcare providers are at the forefront of managing all of these male-specific conditions. Consultation with and referral to specialists, such as urologists, endocrinologists, reproductive specialists, and oncologists, should be carried out as appropriate, and follow-up should be continued with the primary healthcare provider.

DISEASES AND CONDITIONS OF THE PROSTATE

Prostate tissue undergoes changes as men age, and as such, prostatic conditions predominantly occur in older men. The three primary problems related to the prostate are prostatitis, BPH, and prostate cancer. These conditions can be challenging to diagnose because lower urinary tract symptoms, such as frequency, urgency, and dysuria, can be associated with all three conditions. Furthermore, the most serious of the prostate conditions—prostate cancer—usually produces no symptoms in the early stage of the disease. In addition to the diagnostic challenge created by similar, or no, symptoms, the interpretation of prostate-specific antigen (PSA) levels is difficult, and decisions regarding who and when to screen for prostate cancer are not easy.

PROSTATITIS

Inflammation of the prostate is classified into four categories according to a system developed by the National Institutes of Health (NIH) International Prostatitis Collaborative Network [59]. These categories are:

- Acute bacterial prostatitis
- Chronic bacterial prostatitis
- Chronic prostatitis (nonbacterial)/chronic pelvic pain syndrome (subcategorized as A [inflammatory] and B [noninflammatory])
- Asymptomatic inflammatory prostatitis

Both acute and chronic bacterial prostatitis occur in approximately 5% to 10% of men with symptoms related to prostatitis. Chronic nonbacterial prostatitis/chronic pelvic pain syndrome is the most common type, occurring in approximately 90% of symptomatic men [60]. These three types of prostatitis are addressed here; asymptomatic inflammatory prostatitis is an incidental finding during evaluation of another genitourinary condition such as prostate cancer or infertility [61].

It has been estimated that prostatitis accounts for approximately 2 million outpatient visits per year in the United States, with a direct cost of care of nearly $4,000 per patient per year [61]. The condition can have a substantial impact on the quality of life, causing pain and sexual dysfunction, as well as decreased libido and erectile and ejaculatory dysfunction [62; 63].

Chronic prostatitis/chronic pelvic pain syndrome has the greatest impact on the quality of life of all types of prostatitis. Studies have found that the effect of chronic pelvic pain syndrome on the quality of life is similar to that of angina, congestive heart failure, diabetes mellitus, and Crohn disease [61]. Symptoms fluctuate over time; one study showed that 43% of men had symptoms within 11 months of follow-up, and another showed that 31% of men had moderate or marked improvement during two years of follow-up [64; 65]. Chronic prostatitis/chronic pelvic pain syndrome also causes patient anxiety at the initial visit. Most men with symptoms worry that they have an infection (71%) or cancer (68%), and concerns at one-year follow-up have included worsening symptoms without treatment, cancer, infection, and need for surgery [65]. These concerns have led to an increased number of physician visits [65].

Prevalence

The prevalence of prostatitis has been reported to be approximately 8%, ranging from about 2% to 10% [66]. In patients younger than 35 years of age, the most common variant of the syndrome is acute bacterial prostatitis. Among older patients, nonbacterial prostatitis (NIH types II and IV) is the most common [67]. The results of studies have suggested that the symptoms of prostatitis increase the risk for BPH, lower urinary tract symptoms, and prostate cancer [66].

Etiology

The cause of acute and chronic bacterial prostatitis is usually lower urinary tract infection with gram-negative organisms, most notably *Escherichia coli* [60; 61]. Most men with prostatitis, however, have no evidence of urinary tract infection [61]. Other causes may include a primary voiding dysfunction problem; presence of *Chlamydia trachomatis*, *Ureaplasma* species, or *Trichomonas vaginalis*; uncommon organisms (e.g., *Mycobacterium tuberculosis*); HIV; cytomegalovirus; and inflammatory conditions (e.g., sarcoidosis) [67].

The risk factors for prostatitis have not been clearly defined. In a study of 463 men with chronic prostatitis/chronic pelvic pain and 121 asymptomatic age-matched controls, the lifetime prevalence of several self-reported medical conditions were significantly greater among men with prostatitis, specifically neurologic disease (41% vs. 14%); hematopoietic, lymphatic, or infectious disease (41% vs. 20%); psychiatric conditions (29% vs. 11%); nonspecific urethritis (12% vs. 4%); and cardiovascular disease (11% vs. 2%) [68]. The authors of that study noted that more research is needed to determine if such conditions contribute to the pathogenesis of chronic prostatitis/chronic pelvic pain. A history of STIs has been noted to be associated with an increased risk for prostatitis symptoms [66].

Diagnosis

Several other urogenital conditions should be considered in the differential diagnosis of prostatitis, including BPH, cystitis, erectile dysfunction, prostate cancer, STI, and urolithiasis [69; 70; 353]. Of the four types of prostatitis, acute bacterial prostatitis is the easiest to diagnose and treat. Patients with acute prostatitis present with irritative symptoms (dysuria, urinary frequency, and urgency), and obstructive voiding symptoms (hesitancy, incomplete voiding, straining to urinate); the syndrome may also include signs of systemic infection, such as chills and fever [70; 353]. Pain most commonly occurs in the prostate/perineum and scrotum and/or testes; pain referred to the penis or lower back also occurs [70]. Urine samples should be cultured to determine the causative micro-organism.

Chronic bacterial prostatitis is distinguished from acute disease by time, being defined by persistence of symptoms for at least three months, and systemic symptoms are usually absent [58; 70]. The condition should be suspected when the patient's history includes recurrent urinary tract infections, usually with the same bacterial strain [61]. The patient should complete an NIH Chronic Prostatitis Symptom Index to obtain a baseline score for the severity of symptoms [59]. This index includes questions related to three domains—pain, urinary symptoms, and quality-of-life impact—and has been shown to be a valid, reliable tool for measuring prostatitis symptoms [70; 71]. Computed tomography (CT) can determine if there are structural or functional abnormalities of the urinary tract [60; 61].

The diagnostic evaluation for acute or chronic bacterial prostatitis includes a urinalysis and urine culture [61; 70]. When acute prostatitis is suspected, digital rectal exam should be performed gently so as not to precipitate bacteremia and sepsis. The prostate will usually be enlarged, boggy, and tender, though absence of tenderness on initial examination does not exclude the diagnosis of prostatitis. There are no standardized criteria for the diagnosis of chronic prostatitis/chronic pelvic pain syndrome [61; 69]. The Meares-Stamey four-glass test was developed in the late 1960s to screen for prostatitis; the test involves collecting urine samples before and after prostatic massage, as well as collecting prostatic fluid during the massage [72]. Cultures are done on the specimens, and the presence of micro-organisms in the prostatic fluid indicates chronic prostatitis [61; 72]. The accuracy and reliability of the test has not been established, and studies have shown that the test is not used often, even by urologists [61; 69]. There is also a two-glass version of the test that has correlated well with the four-glass version, but that, too, is not often used [61]. The Meares-Stamey test is not helpful for diagnosing chronic pelvic pain syndrome. Men who have substantial lower urinary tract symptoms and pelvic pain may be candidates for urodynamic evaluation, as voiding dysfunction is common in such cases [61].

Treatment Options

No U.S.-based guidelines have been developed, to date, for the treatment of prostatitis, but the European Association of Urology included recommendations for the treatment of prostatitis in its 2008 guidelines on the management of urinary and male genital tract infections [70]. Most patients with bacterial prostatitis can be managed as outpatients with oral antibiotics (e.g., a fluoroquinolone or trimethoprim-sulfamethoxazole) and close follow-up. Hospitalization and broad-spectrum parenteral antibiotics (e.g., piperacillin/tazobactam or ceftriaxone plus ciprofloxacin) should be considered in patients who are systemically ill, are unable to urinate voluntarily, or have risk factors for antimicrobial resistance [70; 353]. An aminoglycoside may be added to any of these antibiotics as initial therapy [70]. A fluoroquinolone is the preferred choice for oral therapy because of the spectrum of antibacterial activity and good penetration into prostatic tissue. Duration of antibiotic treatment should be individualized in relation to duration of symptoms and clinical response; 10 to 14 days will suffice for most acute cases of prostatitis, but 21 to 28 days may be required for those with a more subacute onset or slow resolution of symptoms.

For chronic bacterial prostatitis, the choice of antibiotic depends on the sensitivity of the micro-organism, and the antibiotic should be one that penetrates the prostate [61]. The typical first-line treatment is a four- to six-week course of a fluoroquinolone, and treatment is usually more effective if begun soon after symptoms begin [61; 70; 73; 74]. Trimethoprim-sulfamethoxazole may also be considered [70].

Treatment for chronic prostatitis/chronic pelvic pain syndrome is complex; evidence on the effect of traditional treatment options has been conflicting, and treatment options are often not effective in managing symptoms. The most commonly studied pharmacologic options are antibiotics, alpha-blockers, anti-inflammatory agents, steroid inhibitors, and muscle relaxants, and often, a combination of these agents provides the most effective management [74]. Antibiotics, particularly fluoroquinolones, have improved symptoms, even in some patients in whom a bacterial cause has not been identified [74]. Studies have shown that an antibiotic and an alpha-blocker is more effective than an antibiotic alone [70]. A meta-analysis showed that alpha-blockers, antibiotics, and a combination of the two all significantly improve symptoms (according to scores on the NIH Chronic Prostatitis Symptom Index), with the combination providing the greatest benefit [75]. However, another meta-analysis showed that these same agents—alone and in combination—were not associated with a statistically or clinically significant decrease in symptom scores [76]. The combination of an alpha-blocker (doxazosin) with an anti-inflammatory agent (ibuprofen) and a muscle relaxant (thiocolchicoside) led to a statistically and clinically significant reduction in the total score on the NIH Chronic Prostatitis Symptom Index in one systematic review; according to the findings of another systematic review, the three-agent combination was not superior to monotherapy [74; 76]. Researchers have cautioned that publication bias may cause overestimation of the beneficial effects of alpha-blockers and that the placebo effect has been significant in many studies [75; 76]. Addressing a hypothesis that the pain related to chronic prostatitis may have a neuropathic origin, pregabalin has been evaluated as a management strategy, but a systematic review found that the drug did not improve symptoms and caused side effects in a large percentage of men [77].

Trigger point release/paradoxical relaxation training to release trigger points in the pelvic floor musculature was found to significantly improve symptoms in men who had chronic prostatitis/chronic pelvic pain syndrome [63]. Seventy percent of the men in the study had a significant decrease in the score on the NIH Chronic Prostatitis Symptom Index, with improvement in pelvic pain, urinary symptoms, libido, ejaculatory pain, and erectile and ejaculatory dysfunction [63].

BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH), also referred to as benign prostatic hypertrophy, is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone [78]. BPH is one of the most common conditions among aging men. The onset of lower urinary tract symptoms usually begins after 40 years of age, increasing in prevalence and severity with age [78].

Serious complications and mortality are rare, but the condition has an impact on the quality of life, with symptoms that interfere with normal daily activities and sleep [78]. Complete evaluation is necessary for an accurate diagnosis of BPH; the condition must be differentiated from prostate cancer, which is associated with similar early symptoms. In addition, early detection of BPH leads to early treatment, which can control progression of the disease, preventing such complications as urinary tract infection, acute urinary retention, and obstructive nephropathy [79].

Prevalence and Etiology

What are established risk factors for benign prostatic hypertrophy (BPH)?

The prevalence of BPH increases with age, from approximately 8% of men 31 to 40 years of age to approximately 90% of men in their 80s [80; 81]. Risk factors identified in one study included increased age, prostatic volume, and peak urinary flow rate [82]. Other factors, including some that are modifiable, include obesity, diet, dyslipidemia, hypertension, alcohol use, and smoking [83]. The relative risk for BPH (and common comorbidities) may be higher for Black and Hispanic men than for White men and is thought to be related in part to genetic differences based on race/ethnicity; however, observational studies have produced variable results [81; 84].

Diagnosis

As previously noted, distinguishing BPH from other prostate-related diseases is often difficult, as lower urinary tract symptoms are similar for a variety of conditions. The American Urological Association (AUA) evidence-based guidelines for the management of BPH, updated in 2021, recommend the following tests [78]:

- Medical history
- Assessment of lower urinary tract symptoms
- Determination of severity and bother of symptoms
- Physical examination
- Urinalysis

Determination of a serum PSA level is also recommended if the patient has a life expectancy of more than 10 years (and the diagnosis of prostate cancer will alter management), and a frequency-volume chart is recommended if substantial nocturia is a predominant symptom [78]. Routine measurement of a serum creatinine level is not recommended as part of the initial evaluation of men with lower urinary tract symptoms related to BPH [78].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Institute for Health and Care Excellence recommends offering men with lower urinary tract symptoms information, advice, and time at initial assessment to decide if they wish to have prostate-specific antigen (PSA) testing if their symptoms are suggestive of benign prostatic enlargement.

(https://www.nice.org.uk/guidance/cg97. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

In obtaining a history, clinicians should ask about urinary tract symptoms, sexual function, previous surgical procedures, and general health issues in an attempt to identify other causes of voiding dysfunction or comorbidities that may complicate treatment. Diabetes, cerebrovascular disease, and Parkinson disease can cause urinary symptoms secondary to neurogenic bladder, and STIs or trauma may cause urethral stricture [85]. It may be appropriate to have the patient keep a diary of voiding habits (frequency, volume, etc.) [78].

Assessment of symptoms is an integral aspect of the initial evaluation for BPH, as it helps to determine the severity of disease. The International Prostate Symptom Score (IPSS) (previously called the AUA Symptom Index) is a validated, self-administered symptom frequency and severity assessment questionnaire originally developed by the AUA Measurement Committee [78]. The IPSS is a widely available, seven-question assessment tool that has been validated for clarity, test/retest reliability, internal consistency, and criteria strength [78; 86]. The IPSS addresses [86]:

- Urinary frequency
- Hesitancy
- Nocturia
- Incomplete emptying
- Urgency
- Weak urinary stream
- Intermittence

Symptoms should be discussed with the patient and questions addressed as necessary [78].

The physical examination should include a digital rectal examination (DRE) to determine the size, consistency, and shape of the prostate [78]. A symmetrically firm and enlarged prostate by DRE is indicative of BPH [79]. The true size of the prostate is often underestimated by DRE compared with transrectal ultrasound [78]. Examination should also include neurologic evaluation to assess the patient's general mental status, ambulatory status, neuromuscular function of the lower extremities, and anal sphincter tone [78].

A urinalysis (dipstick test) to screen for hematuria, proteinuria, pyuria, and other abnormalities can help to rule out such conditions as bladder cancer, carcinoma in situ of the bladder, urinary tract infection, urethral strictures, distal urethral stones, and bladder stones, which are less likely if the results of urinalysis are normal [78].

Optional studies that may be used to confirm the diagnosis or evaluate the presence and severity of BPH include post-voiding residual urine measurement (PVR) and uroflowmetry studies [78]. A PVR is useful in determining a baseline ability of the bladder to empty and detecting severe urinary retention that may not be amenable to medical therapy. Uroflowmetry is a simple, office-based procedure, an adjunct to evaluation of lower urinary tract symptoms and probability of bladder outlet obstruction. Flow rates of <10 mL/second have shown a specificity of 70%, a positive predictive value of 70%, and a sensitivity of 47% for bladder outlet obstruction [78].

Treatment Options

According to the AUA guideline, the benefits, risks, and costs of treatment options should be discussed with patients who have moderate-to-severe symptoms (IPSS score of 8 or more) who are bothered enough by the symptoms to consider therapy [78]. The treatment options for BPH include:

- Watchful waiting
- Medical therapy (minimally invasive procedures)
- Surgical interventions

The AUA guideline recommends watchful waiting as the preferred approach for men who have mild symptoms (a score of less than 8 on the AUA Symptom Index) [78]. This approach may also be taken for men with moderate-to-severe symptoms (score of 8 or more) who are not bothered by the symptoms and have no complications [87]. Watchful waiting should include yearly evaluations similar to the initial one [78]. Lifestyle changes and behavioral interventions are considered reasonable first-line treatments for all patients. Symptoms may be reduced by avoiding decongestants and antihistamines, decreasing fluid intake (and avoiding caffeine and alcohol) prior to bedtime, and increasing physical activity and weight loss [78].

AUA guidelines recommend offering monotherapy with an alpha-blocker as initial preferred option for patients with bothersome -to-severe symptoms [78]. Clinicians should consider performing a PVR measurement or uroflowmetry prior to treatment intervention. Five alpha-blockers have FDA-approved indications for BPH (***Table 5***). Clinical studies show that all five of these drugs—alfuzosin, doxazosin, tamsulosin, terazosin, and silodosin—are equally effective in terms of symptom relief and expected range of improvement in symptom index (IPSS) score [78]. The choice of alpha-blocker should be based on the patient's age and comorbidities, and different adverse event profiles (e.g., ejaculatory dysfunction, changes in blood pressure).

The adverse events associated with alpha-blockers are orthostatic hypotension, dizziness, fatigue (asthenia), and ejaculatory problems [78]. These drugs should not be used for men who are taking medication for erectile dysfunction, as the interaction between the two drugs can cause profound hypotension [79]. Alpha-blocker agent use also has been associated with the rare complication of intraoperative floppy iris syndrome; patients anticipating cataract surgery should be informed of the risks and advised to discuss these risks with their ophthalmologist [78].

Two 5-alpha reductase inhibitors, finasteride and dutasteride, are also approved for treatment of BPH-related symptoms and are recommended options in the AUA guideline [78]. This is less effective than therapy with alpha-adrenergic antagonists for relieving lower urinary tract symptoms, leading to an average improvement of 3 points on the AUA Symptom Index [78]. The advantage of 5-alpha reductase inhibitors is that they also act to prevent progression of disease and reduce the size of the prostate. As such, the AUA notes that these drugs should be used only for men who have evidence of prostatic enlargement [78]. Men should be made aware of the need for long-term therapy with either of these drugs, and clinicians should also discuss the possible adverse events, which include decreased libido, ejaculatory dysfunction, and erectile dysfunction. These effects usually resolve within one year [78; 79].

In 2011, the FDA issued a safety announcement that the Warnings and Precautions section of the labels of 5-alpha reductase inhibitors was revised to include new safety information about the increased risk of a diagnosis of high-grade prostate cancer [92]. The revision came after FDA review of two prostate cancer prevention trials, in which finasteride and dutasteride reduced the incidence of lower risk forms of prostate cancer but were associated with an increased incidence of high-grade prostate cancer [92].

The AUA guideline also supports the use of combination therapy with an alpha-blocker and a 5-alpha reductase inhibitor for men with lower urinary tract symptoms and evidence of prostate enlargement, as demonstrated on volume measurement, PSA level as a proxy for volume, or on DRE [78]. A fixed-dose combination of dutasteride (0.5 mg) and tamsulosin (0.4 mg) is available, and the results at four years showed that, for men with a baseline prostate volume ≥40 mL and PSA level of ≥1.5 ng/mL, the combination led to greater reductions in the relative risk of clinical progression, acute urinary retention, or BPH-related surgery than either drug alone [93].

The AUA guideline also notes that anticholinergic agents are appropriate and effective options for managing BPH-related symptoms in men who do not have an elevated post-void residual and when symptoms are predominantly irritative [78].

PHARMACOLOGIC THERAPY FOR BENIGN PROSTATIC HYPERTROPHY	
Agent	**Daily Dose**
Alpha-blockers	
Alfuzosin ER (Uroxatral)	10 mg
Doxazosin (Cardura) and doxazosin ER (Cardura XL)	4–8 mg
Silodosin (Rapaflo)	8 mg
Tamsulosin (Flomax)	0.4–0.8 mg
Terazosin (Hytrin)	1–2 mg
5-alpha reductase inhibitors	
Dutasteride (Avodart)	0.5 mg
Finasteride (Proscar)[a]	5 mg
Combination (alpha-blocker and 5-alpha reductase inhibitor)	
Dutasteride/tamsulosin (Jalyn)	1 capsule (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride)
Phosphodiesterase 5 inhibitors	
Tadalafil (Cialis)[a]	5 mg
[a]Combination finasteride/tadalafil (5 mg each) may also be used.	
Source: [89; 90; 91]	*Table 5*

Phosphodiesterase type-5 inhibitors have also been shown to be effective for reducing the symptoms associated with BPH [94]. This class of drugs also offers advantages over other drugs in its rapid onset of action, fewer adverse events, and enhanced sexual function [94]. Potential adverse events include back pain, dyspepsia, headache, and dizziness [95]. In 2011, the first phosphodiesterase type-5 inhibitor—tadalafil—was approved by the FDA for BPH-related symptoms, with indications for symptoms in men who have prostate enlargement, with or without erectile dysfunction [95]. Before prescribing tadalafil, clinicians should ensure that patients are not taking drugs that interact with tadalafil, such as nonselective alpha-blockers, nitrates, and cytochrome P450 inhibitors [95].

Saw palmetto, a commonly used alternative therapy for BPH, is not recommended for BPH-related symptoms, as the most recent data have shown no clinically meaningful effect on symptoms [78].

Minimally invasive therapies such as transurethral needle ablation and transurethral microwave thermotherapy are treatment options for men with bothersome moderate or severe symptoms [78]. However, the AUA guideline notes that, although these therapies improve symptoms, flow rate, and quality of life, the outcomes are not as good as those after transurethral resection of the prostate [78].

Surgical interventions are typically reserved for worsening disease and severe symptoms that do not respond to medical treatment. The AUA guideline recommends surgery for patients with renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections, bladder stones, or gross hematuria due to BPH; or symptoms refractory to other therapies [78]. The most common procedure is transurethral resection of the prostate, which comprises 90% of all prostate surgeries done for BPH and is the benchmark for therapy [78; 96]. Open prostatectomy; transurethral laser ablation or enucleation; laser resection; photoselective vaporization; and transurethral incision, vaporization, and resection are other surgical options, and the selection of intervention is based on the surgeon's experience, the patient's anatomy, and a discussion of the benefits and risk of complications [78].

PROSTATE CANCER

Prostate cancer is the most commonly diagnosed cancer among men, accounting for 19% of all cancer diagnoses in men and the second leading cause of cancer-related deaths, responsible for 9% of cancer-related deaths in men [16]. The lifetime risk of a prostate cancer diagnosis is approximately 15% [16].

Prostate cancer is a complex issue for both men and their healthcare providers for many reasons, including variation in tumor biology, lack of specific symptoms, accuracy of levels of PSA and its several derivatives, questions about optimum treatment, and, most notably, controversy surrounding screening.

Prevalence and Etiology

In 2022, the estimated projected number of new prostate cancer diagnoses was 268,490, with 34,500 prostate cancer-related deaths [16]. The majority of newly diagnosed prostate cancers have localized disease. The highest incidence is found among Black men (172.6 per 100,000), and the lowest is among Asian American and Pacific Islander men (55.0 per 100,000) [16]. The death rate related to prostate cancer is also highest for Black men, with a rate that is more than twice that for men of all other races/ethnicities (37.9 per 100,000 vs. 17.8 [White], 21.0 [American Indian and Alaska Native], 15.6 [Hispanic/Latino], and 8.6 [Asian American and Pacific Islander]) [16]. The mortality rate associated with prostate cancer decreased 4.1% per year between 2009 and 2019, in part, because of improvements in early detection and treatment [16].

The known risk factors for prostate cancer are advanced age, Black race, and a family history of the disease (especially when diagnosed at a younger age) [16; 97]. The risk for prostate cancer may also be increased for men with symptoms of prostatitis [66].

Prevention

Several studies have been undertaken to determine the efficacy of chemoprevention agents and dietary supplements to reduce the risk of prostate cancer. The chemoprevention agents evaluated belong to the class of 5-alpha reductase inhibitors, a class of drugs approved for the treatment of BPH. One drug in this class, finasteride, was evaluated in the first large-scale chemoprevention study, the Prostate Cancer Prevention Trial (PCPT), a seven-year study involving nearly 19,000 men 55 years of age or older. In that study, finasteride significantly reduced the prevalence of prostate cancer (18% vs. 24% for the placebo group) [98]. Dutasteride was shown to decrease the risk of prostate cancer in the REDUCE trial, and extended follow-up indicated a low rate of new prostate cancer diagnoses [99; 100]. The initial results of the PCPT and REDUCE trials led the American Society of Clinical Oncology (ASCO) and the AUA to develop a joint guideline recommending finasteride and dutasteride for the prevention of prostate cancer [90]. However, reanalysis of the results of the trials showed that the risk for high-grade prostate cancer was increased and the reduction in prostate cancer risk was seen primarily for less fatal subtypes of prostate cancer that are often not treated [100; 101]. In 2011, the FDA decided against approving the two drugs for the prevention of prostate cancer, noting that the risk-benefit profile is not favorable for chemoprevention [91; 101; 102]. As stated earlier, the FDA revised the labels of all 5-alpha reductase inhibitors to note the increased risk of higher-grade prostate cancer associated with the drugs [92]. The ASCO/AUA guideline was withdrawn, and experts have called for more research to determine whether 5-alpha reductase inhibitors have a role in the prevention of prostate cancer [101; 102; 103].

Dietary supplements have not been shown to substantially reduce the prevalence of prostate cancer. In the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized study of more than 35,000 men, neither of those two vitamins, alone or in combination, prevented prostate cancer in relatively healthy men [104]. A subsequent phase III trial showed that selenium supplementation had no effect on prostate cancer risk among men with high-grade prostatic intraepithelial neoplasia [105]. There is insufficient evidence for the routine recommendation of other dietary supplements, such as soy, milk thistle, omega fatty acids, lycopene, or green tea, to prevent prostate cancer [106; 107; 359].

Screening

What is the primary benefit of prostate cancer screening?

There is no question that available screening methods and enhanced awareness has led to an increased number of men in whom prostate cancer is diagnosed at an earlier stage. The primary benefit of screening is a lower stage and grade of cancer at the time of diagnosis, and the high rate of localized disease at the time of diagnosis (92% to 96%) reflects, in part, the increased number of cancers that are detected earlier through screening [102; 108; 109]. Despite this benefit, an effect of screening on mortality has not been clearly demonstrated. After 13 years of follow-up in the National Cancer Institute's Prostate, Lung, Colon, and Ovary (PLCO) trial, there was no benefit of annual screening on mortality [110]. A meta-analysis (five randomized controlled trials) similarly demonstrated no effect of screening on prostate cancer-specific or overall mortality [111]. However, data from the European Randomized Study of Screening for Prostate Cancer demonstrated that screening reduced the risk for prostate cancer death by 7% to 9% per year [112].

In addition to a lack of effect on mortality, screening is associated with high rates of false-positive results, overdiagnosis and subsequent overtreatment, and complications. Among men who had four PSA tests, the cumulative risk for at least one false-positive result was 12.9% [102]. Rates of overdiagnosis have been estimated at 17% to 50%, and 23% to 42% of all screen-detected prostate cancers are overtreated [102; 113]. Furthermore, treatment is associated with complication rates of 20% to 50% [102; 114]. These findings led several expert panels to update their screening recommendations (***Table 6***) [97; 102; 108; 114; 115; 116; 117]. Overall, experts recommend against routine screening for most men and emphasize the need to consider life expectancy and the patient's age

RECOMMENDATIONS FOR PROSTATE CANCER SCREENING			
Organization	**Year of Publication**	**Screening Recommendation**	**Notes**
American Cancer Society	2010	—	Discuss the potential benefits, risks, and uncertainties associated with prostate cancer screening with men ≥50 years
American Society of Clinical Oncology	2012	Discourage general screening for men with a life expectancy of ≤10 years, as the harms outweigh the benefits	Discuss the individual appropriateness of screening with men who have a life expectancy >10 years
American Urological Association	2013, reconfirmed 2018	No routine screening in men 40 to 54 years of age at average risk	Decisions should be individualized for men younger than 55 years who are at high risk. Shared decision-making should take place for men 55 to 69 years of age, for whom screening is of greatest benefit.
American College of Physicians	2013	No routine screening with PSA for average-risk men younger than 50, men older than 69, or men with a life expectancy of less than 10 to 15 years	Clinicians should inform men 50 to 69 years of age about limited potential benefits and substantial harms of screening and should individualize decision based on patient's general health, life expectancy, and preferences.
U.S. Preventive Services Task Force	2018	No routine screening for men 70 years of age and older. For men 55 to 69 years of age, the decision should individualized.	Clinicians should discuss the potential benefits and harms of screening.
National Comprehensive Cancer Network	2022	—	Offer baseline PSA testing (with DRE) to average-risk men 45 to 75 years of age, or 40 to 75 years of age for Black/African American men and those with germline mutations that increase risk. If serum PSA values <1 ng/mL, repeat screening every 2 to 4 years. Consider PSA testing only in very healthy patients older than 75 years of age.
Source: [97; 102; 108; 114; 115; 116; 117]			*Table 6*

and risk factors for the disease. The age to start a discussion about screening varies slightly among the guidelines. The AUA guideline notes that decisions about screening should be individualized for men younger than 55 years who are at high risk for the disease (positive family history or Black race) [114]. The guideline also states that the greatest benefit of screening appears to be for men 55 to 69 years of age and strongly recommends shared decision making for men in this age-group. The ACS guideline notes that screening should be discussed beginning at 50 years of age for men at average risk and before 50 years of age for men at higher risk [108]. The NCCN guideline suggests that clinicians talk to patients about the risks and benefits of a baseline DRE and PSA beginning at 40 years of age [97]. The American College of Physicians (ACP) recommends that clinicians inform their male patients, 50 to 69 years of age, about the limited potential benefits and substantial harms of screening [115].

Researchers continue to investigate ways to make screening more effective. Using a higher PSA threshold for biopsy for older men and less frequent screening for men with low PSA levels are strategies that may reduce the risk of overdiagnosis as well as prostate cancer-related mortality [118].

Informed decision making is integral in selecting approaches to screening, with every guideline emphasizing the need to discuss the potential benefits, harms, and limitations associated with screening with their male patients. The American Cancer Society notes that men should receive information about screening directly from their healthcare provider or be referred to reliable and "culturally appropriate" sources [108]. Decision aids can be especially useful in helping men and their healthcare providers weigh the benefits and risks of screening, and studies of decision aids have led to improved knowledge and have increased men's desire for an active role in decision making [108; 114; 119; 120; 121]. The NCCN guideline offers talking points for discussion, and ASCO provides a decision aid tool (https://www.asco.org/sites/new-www.asco.org/files/content-files/practice-and-guidelines/documents/2012-psa-pco-decision-aid.pdf).

Despite the continued emphasis on informed decision making, the percentage of men who report having had a discussion with their healthcare providers about screening has been suboptimal, with a rate of about 63% to 66% of the general male population [122; 123]. Black men were most likely to have had a discussion, and men without a usual source of care were the least likely [123].

For men who choose to have screening for prostate cancer, the combination of DRE and PSA is the preferred method, providing better predictive value than either method alone [102]. The sensitivity of PSA testing is higher than that of DRE, especially for tumors that are more aggressive [109]. However, the PSA level can vary as a result of several factors.

PSA and Its Derivatives

In an effort to enhance the specificity of PSA testing, variations of the PSA test have been developed, including free PSA, PSA density, PSA velocity, and complexed PSA [97]. Each has its benefits and limitations, and the AUA notes that none increases the benefits-harms ratio of screening [114]. Levels of free PSA have been shown to be significantly lower in men with prostate cancer than in men without the disease [97]. The FDA has approved percent-free PSA for the early detection of prostate cancer in men with PSA levels between 4 ng/mL and 10 ng/mL [97].

PSA density is the result of dividing the PSA level by the volume of the prostate, as measured by transrectal ultrasonography, and a higher result suggests a greater likelihood of prostate cancer [97]. Greater PSA density has correlated with the presence of prostate cancer, as well as with the pathologic stage of the tumor and its aggressiveness and progression after treatment [124]. The use of PSA density has been limited by the lack of precision of total PSA, of measurement of prostate volume, and of the need to carry out transrectal ultrasonography [97]. In addition, PSA density does not offer much benefit compared with other PSA derivatives [97]. PSA velocity is the rate at which a PSA level increases over a period of time, and it has been most helpful for longitudinal monitoring of men younger than 50 years of age who have normal PSA levels and no prostate enlargement [97]. A high PSA velocity alone should not prompt biopsy but instead, aid in decision making [97]. The test is not useful for men with PSA values greater than 10 ng/mL [97]. The ratio of complexed PSA to total PSA provides information comparable to the ratio of free to total PSA, and the use of complexed PSA has been approved as a detection aid (in conjunction with DRE) for men 50 years of age or older; however, the test is not widely used in practice [97].

Threshold for Biopsy

Prostate cancer is found in about 25% of biopsy specimens, illustrating a problem regarding a well-defined threshold at which to obtain a biopsy specimen [125]. Although most cancer is detected with use of a PSA threshold of 4 ng/mL, some studies have shown that prostate cancer is subsequently found in men with levels in the range of 2.5–4.0 ng/mL [97]. The NCCN concluded that while these values have been used by many, a level of 3.0 ng/mL is supported by trials and would more robustly limit the risk of overdetection. However, there was not a consensus among NCCN panel members regarding limiting the option to biopsy to prespecified PSA thresholds [126]. The NCCN panel also concluded that DRE alone is not an absolute indication for biopsy in men with low PSA, as the positive predictive value of DRE in this population is poor. However, a very suspicious DRE, independent of PSA, could indicate high-grade cancer in men with normal PSA values, and therefore, biopsy should be considered in these men [126].

Diagnosis and Staging

Men with early prostate cancer are usually asymptomatic. More advanced disease may be associated with changes in urinary habits, such as a slowing of the urinary stream, sense of incomplete voiding, nocturia, and frequency, as well as dysuria, hematuria, or pain in the lower back or pelvis. Because many of these symptoms are similar to those linked to benign prostate conditions, prostate cancer cannot be diagnosed on symptoms alone. The diagnostic methods are the same as those used for screening: PSA, DRE, and transrectal ultrasonography. In performing the DRE, the clinician should focus on the size, consistency, and abnormalities within or beyond the gland. Prostate cancers are characteristically hard, nodular, and irregular.

CLASSIFICATIONS OF RISK OF BIOCHEMICAL RECURRENCE				
Risk Level	**Tumor**	**Gleason Score**	**PSA Level (ng/mL)**	**Other**
Very low	T1c	≤6	<10	Biopsy cores: <3 positive, ≤50% cancer in any core PSA density: <0.15 ng/mL/g
Low	T1–T2a	≤6	<10	—
Intermediate	T2b–T2c	7 (or PSA level as noted)	10–20 ng/mL	—
High	T3a (or other criteria)	8–10 (or other criteria)	>20	—
Very high	T3b–T4 (locally advanced)	Primary Gleason pattern 5 (or other criteria)	—	Biopsy cores: >4 with Gleason score 8–10
NCCN = National Comprehensive Cancer Network, PSA = prostate-specific antigen.				
Source: [126]				*Table 7*

In its 2013 Best Practice Statement on PSA, the AUA emphasizes the importance of PSA in staging, noting that the PSA level predicts response of prostate cancer to local therapy [127]. Response is most likely in men with a PSA level <10 ng/mL [127].

Biopsy of the prostate with analysis of the tissue provides the most definitive diagnostic procedure. It also gives evidence of the aggressiveness of the tumor when cancer is detected. The pathologist quantifies the aggressiveness of the tumor with use of the Gleason score, assigning a number between 2 and 10 (with 10 representing the most aggressive). Pathologic review involves both staging according to the American Joint Committee on Cancer staging manual and classification of the tumor with the Gleason score [128]. Further staging with imaging (CT, MRI, bone scan) is done only for tumors that are confined to the prostate with a Gleason score of 8 or higher or a PSA level of greater than 20 ng/mL or for tumors that extend beyond the prostate or are symptomatic [97]. As part of the Choosing Wisely campaign, the AUA notes that a routine bone scan is not necessary for men with newly diagnosed prostate cancer with a PSA level <20.0 ng/mL and a Gleason score of ≤6 [127].

Treatment Options

Recognizing that many prostate cancers have an indolent natural history, guidelines recommend utilization of a risk stratification classification for patients with newly diagnosed localized disease [358]. Stratification facilitates patient counseling and should be used with a shared decision-making approach in which treatment decisions are based on the patient's estimated life expectancy and the risk of biochemical recurrence [126]. Risk of biochemical recurrence has been classified by the NCCN into five categories (***Table 7***) [126].

A new prostate cancer grading system was developed during a 2014 consensus conference of the International Society of Urological Pathology (ISUP). The new system resulted in changes to the assignment of Gleason pattern based on pathology. This system assigns grade groups from 1 to 5, derived from the Gleason score. Many experts believe that the ISUP grade groups enable patients to better understand their true risk level and limit overtreatment. The NCCN has accepted the new grade group system. Patients remain divided into very-low-, low-, intermediate-, high-, and very-high-risk groups [126].

The primary options for localized prostate cancer are watchful waiting (also known as active surveillance), radiation therapy (either three-dimensional external-beam radiation or brachytherapy), and radical prostatectomy. Other options include androgen-deprivation therapy (ADT, also referred to as hormone therapy), chemotherapy, cryosurgery, and immunotherapy.

Each treatment option is associated with benefits and harms, and clinicians should discuss each option in detail and provide educational resources and decision aids [129; 130; 131]. To gain a true understanding of a patient's preferences, treatment options should be discussed only after the patient has described his preferences [132]. Clinicians should carefully assess their patients' understanding of treatment options; studies of underserved men have shown low comprehension of common terms used in prostate cancer treatment discussions [133; 134]. Attention should also be paid to how to best communicate risk. A study has shown that such terms as "number needed to treat," "odds ratio," and "relative risk reduction" were confusing to men [135]. In that study, men best understood information when it was presented as

ADVANTAGES AND DISADVANTAGES OF ACTIVE SURVEILLANCE FOR PROSTATE CANCER	
Advantages	**Disadvantages**
Ensure that small indolent cancers are not treated unnecessarily	Lack of definitive prompt for treatment may lead to missed opportunity for cure
Avoid side effects of treatment that may be unnecessary	Cancer may progress or metastasize before treatment
Maintain quality of life and normal activities	Treatment of larger, more aggressive cancer may be more complex, with increased side effects
Decrease initial costs	Living with an untreated cancer increases anxiety Must carry out frequent medical examinations and biopsies Timing and value of long-term natural history of untreated disease is undetermined Long-term natural history of untreated disease is uncertain
Source: [126]	*Table 8*

an absolute risk reduction and in a positive context; men preferred that treatment options be discussed in terms of the probability of an increase in survival (rather than a decrease in mortality) and that the discussion include the impact of treatment on patient-centered quality-of-life outcomes [135].

Active Surveillance

Active surveillance has also been referred to as watchful waiting, but the terms have not always been defined the same way, and researchers are calling for a distinction between the two terms. Active surveillance denotes an approach in which men with localized, low-risk prostate cancer are followed up closely for clinical signs that prompt definitive treatment with curative intent should this become necessary [136; 358]. Watchful waiting refers to the strategy recommended for asymptomatic patients with prostate cancer and limited life expectancy [358]. Some studies draw further distinction, defining watchful waiting as observation and provision of palliative care when prostate cancer becomes symptomatic, and active surveillance as close follow-up (with DRE, PSA levels, and biopsies) and provision of treatment at signs of disease progression [138]. Patients with a life expectancy of less than five years do not benefit from prostate cancer screening, diagnosis, or treatment as prostate cancer treatment does not improve survival within five years of follow-up [358].

For patients with favorable intermediate-risk prostate cancer, clinicians should discuss with patients the options of active surveillance, radiation therapy, or radical prostatectomy [358]. Choosing active surveillance rather than definitive treatment is difficult because of the myriad advantages and disadvantages to the approach (***Table 8***) [126]. Data on active surveillance have also conflicted. In a cohort of 450 men followed up for a median of nearly seven years, the rate of prostate cancer-specific mortality was low [139]. Two later systematic reviews indicated that the evidence was insufficient to determine whether active surveillance with curative intent was an appropriate option for men with localized prostate cancer [136; 137]. Most recently, radical prostatectomy was compared with active surveillance, and the intervention did not significantly reduce all-cause or prostate cancer-specific mortality through at least 12 years of follow-up [140]. In addition, a cost-effectiveness analysis demonstrated that active surveillance was most effective and least expensive compared with several interventions (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy) [138].

The NCCN Panel recommends active surveillance for all men with very-low-risk prostate cancer and a life expectancy of less than 20 years and believes that surveillance should be considered for men with very-low-risk prostate cancer and a life expectancy of 20 years or more [126]. In addition, the Panel recommends active surveillance for all men with low- and favorable intermediate-risk prostate cancer and a life expectancy of less than 20 years and believes that it should be considered for men with low- and favorable intermediate-risk and a life expectancy of 10 years or more [126]. With active surveillance, recommended monitoring is measurement of a PSA level no more than every 6 months, unless clinically indicated, and physical exam with DRE every 12 months [126]. An increase in PSA should prompt re-testing as transient PSA elevations are common; serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt re-evaluation with prostate MRI and possible prostate biopsy [126; 358].

Radiation Therapy

Radiation therapy is an option for men at various levels of risk for biochemical recurrence, except for men for whom active surveillance is recommended [126]. Radiation to pelvic lymph nodes may be considered for men with intermediate risk and should be done for men at high risk [126]. Radiation therapy offers progression-free survival similar to that of prostatectomy while avoiding the complications associated with surgery [126].

The advent of three-dimensional (3D) CRT, which integrates external-beam radiation with CT images, has allowed for the delivery of higher radiation doses but with a lower risk of side effects because of enhanced precision [126]. About half of men will have temporary bladder or bowel symptoms during treatment with external-beam radiation therapy [126]. The disadvantage to external-beam radiation therapy is the time needed for treatment, as the recommended duration of treatment is eight to nine weeks [126].

Intensity-modulated radiation therapy (IMRT), a second-generation 3D technique, has been used increasingly in clinical practice [141]. IMRT reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared with 3D-CRT in some retrospective, population-based studies, but treatment cost was increased [142; 143]. More recently, moderately hypofractionated image-guided IMRT regimens have been tested in randomized trials, but additional research is needed [126].

Brachytherapy has been used increasingly for men with early localized prostate cancer; however, increasing evidence suggests that technical advancements in brachytherapy may have a role in treatment of high-risk localized and locally advanced prostate cancer [126; 144; 145]. This approach is a recommended option as monotherapy for men at low risk and a life expectancy of at least 10 years and in combination with external-beam radiation therapy for men at intermediate risk, regardless of life expectancy [126; 146]. Complications are increased when the two forms of radiation therapy are used together [126]. Brachytherapy alone yields control rates comparable to those of surgery (approximately 90%), and added advantages are short treatment duration, minimal risk of incontinence, and short-term preservation of erectile function; the seeds are implanted in one procedure, and men typically recover in one day [126]. Disadvantages include the need for general anesthesia and a risk of acute urinary retention [126].

Radical Prostatectomy

Radical prostatectomy is an option for men with a life expectancy of at least 10 years who have clinically localized disease that can be completely excised [126]. It also may be an option for men with high-risk disease and for select patients with very-high-risk disease, although several factors (e.g., PSA >10 ng/mL, stage T2b or higher, Gleason score 9 or 10, higher number of biopsy cores with high-grade cancer, more than 50% core involvement) predict unfavorable outcome in these patients [147]. Radical prostatectomy is a salvage option for patients experiencing biochemical recurrence after primary external beam radiation therapy, but morbidity remains significantly higher than when the treatment is used as initial therapy [148; 149]. This treatment option has been most often associated with the highest survival rates but also with side effects that have been reported to have a significant impact on quality of life, such as impotence, incontinence, urethral stricture, and surgery-related morbidity [126; 150; 151]. Despite the potential side effects, the sense of being cancer free has led men who chose to have radical prostatectomy to be satisfied with their decision [152]. Laparoscopic and robot-assisted procedures have been found to yield results similar to those for open procedures, but rates of incontinence and erectile dysfunction may be higher [126]. The AUA notes that no conclusive benefit to pelvic lymph node dissection has been found [127]. Such dissection for clinically localized disease may not be necessary if the PSA is less than 10 ng/nL and the Gleason score ≤6 [127].

Androgen Deprivation Therapy (ADT)

What is the recommended initial therapy for metastatic prostate cancer?

ADT involves medical or surgical castration (with luteinizing hormone-releasing hormone [LHRH] agonists or orchiectomy, respectively). It is recommended as an adjunct to radiation therapy or prostatectomy for men with local or locally advanced disease and at high or intermediate risk for recurrence [126]. Meta-analyses have shown clinical benefit for adjuvant ADT after either radiation therapy or prostatectomy or neoadjuvant therapy before radiation therapy [153; 154].

Both NCCN and ASCO recommend ADT as initial treatment for metastatic prostate cancer [126; 155]. Researchers have evaluated the timing of ADT—early (before symptoms occur) or delayed—and early therapy has provided no overall survival benefit and only a modest decrease in risk for prostate cancer-specific mortality; because of this, the ASCO guideline does not make a recommendation for early ADT [155]. Several studies have demonstrated that intermittent ADT is as effective as continuous ADT for metastatic or locally advanced disease, with better quality of life and fewer side effects [156; 157; 158].

Use of ADT as a primary therapy for men with localized prostate cancer has increased significantly among men at low and intermediate risk, but this approach should not be considered standard [126; 146]. ADT is associated with several adverse events, including osteoporosis, increased risk for fracture, obesity, insulin resistance, and increased risk for cardiovascular disease and diabetes [126].

Chemotherapy

The use of chemotherapy is typically reserved for men with metastatic castration-resistant prostate cancer, and docetaxel-based regimens have been shown to confer survival benefit [159; 160]. The duration of therapy is not well-defined, but 10 cycles were used in the phase III trials in which these regimens were evaluated.

Cryosurgery

Cryosurgery is a minimally invasive procedure that is an option for prostate cancer (of any grade) that is clinically confined to the prostate in men at low, intermediate, or high risk [161]. The five-year biochemical disease-free survival rates have ranged from 48% to 92%, depending on the risk of recurrence, but long-term data on prostate cancer-specific survival are not yet available and there are no clearly defined guidelines for patient selection for cryosurgery as a salvage procedure [161]. The authors of a meta-analysis published in 2007 and updated in 2018 concluded that it was difficult to determine the relative benefits of this treatment because of the poor quality of the available studies [162].

Options for Metastatic Castration-Resistant Prostate Cancer

Since 2010, three agents, an immunotherapy, and a radiopharmaceutical have been approved for metastatic castration-resistant prostate cancer. Cabazitaxel (Jevtana), enzalutamide (Xtandi), and abiraterone acetate (Zytiga) are indicated for treatment following docetaxel [126]. Sipuleucel-T (Provenge), an autologous cellular immunotherapy, is approved for men with metastatic castration-resistant prostate cancer who are asymptomatic or minimally symptomatic. Lastly, radium 223 dichloride (Xofigo) was approved in May 2013 for the treatment of metastatic castration-resistant prostate cancer with bone metastases (but not visceral involvement) [126].

Prognosis

Survival after treatment of prostate cancer is related to the extent of the tumor at the time of diagnosis, and the relative five-year survival rate is 100% for localized or regional prostate cancer [16]. The five-year survival rate is substantially lower (30%) when prostate cancer is metastatic at the time of diagnosis [16].

Follow-up

Primary care physicians, nurses, and other healthcare professionals who see patients on a regular basis play an important role in the follow-up evaluation for men who opt for active surveillance, as well as for those who have been treated by an oncologist. After treatment for prostate cancer, men should be followed up with an annual DRE and PSA testing every 6 to 12 months for five years and annually thereafter [163]. Primary care clinicians can also aid in the management of the side effects of treatment and screening for secondary cancers.

Case Study

Patient A is an active man, 59 years of age, who missed his yearly DRE and PSA. The results of these tests had been within normal limits in all previous examinations. At his next examination, a firm prostate nodule, approximately 2 mm in diameter, is palpated, and the PSA level is 14 ng/mL. A needle biopsy of the prostate is performed within one week of the PSA measurement. The biopsy shows several sites containing cells indicative of adenocarcinoma of the prostate, with a Gleason score of between 8 and 9.

After carefully evaluating the treatment options for an aggressive tumor, Patient A chooses radical prostatectomy and seeks care at an institution where nerve-sparing surgery is performed with the assistance of a robotic, computer-controlled device, to help reduce the risk of adverse events. According to the pathologic evaluation, the tumor is an adenocarcinoma that has extended beyond the capsule of the gland but has not involved the seminal vesicles.

Staging studies, including an MRI of the pelvis and abdomen and a bone scan, confirm the extent of the tumor and demonstrate lack of lymph node involvement or distant metastasis (T3a, N0, M0). Because of the T3a finding, a course of external-beam radiation therapy to the local site is prescribed.

At the three-month follow-up visit, the PSA level has increased to 20 ng/mL, and a bone scan demonstrates multiple skeletal lesions, primarily in the ribs, pelvis, and skull, none of which had been seen on the previous scan. Due to the rapid progression of disease and the metastatic lesions, the patient's survival is estimated to be less than three years.

After a discussion with his surgeon, oncologist, and urologist, the patient decides to forego ADT, choosing instead to enroll in a clinical trial for treatment consisting of chemotherapy with docetaxel in combination with the angiogenesis inhibitor bevacizumab over a course of several months. The treatment causes some nausea, malaise, and hair loss, but the patient tolerates the effects well. The primary bothersome adverse effect is oral ulcers, which require topical treatment. The PSA level drops steadily during follow-up, reaching a level of 0.4 ng/mL after approximately six months of treatment.

Patient A continues to feel well after two years of follow-up, and the PSA level has remained at 0.2 ng/mL or less. Incontinence that was present after the surgery has ended, but erectile dysfunction remains, despite the use of medications.

DISTINGUISHING BETWEEN TESTICULAR TORSION AND EPIDIDYMITIS		
Sign/Symptom	**Testicular Torsion**	**Epididymitis**
Onset of pain	Sudden (<12 hours)	Insidious
Cremasteric reflex	Absent	Present
Tenderness	Diffuse; spermatic cord	Epididymal area
Appearance of scrotum	Usually normal	Edematous, "orange peel" appearance
Testicular lie	High	Normal

Source: [164; 165; 167; 168] *Table 9*

DISEASES AND CONDITIONS OF THE TESTES

Testicular conditions are fairly uncommon but are more prevalent among younger men than older men [164; 165]. As with conditions of the prostate, testicular conditions may be associated with similar symptoms, creating a challenge for accurate diagnosis. When evaluating a man who has acute scrotal pain, a primary objective is to distinguish benign conditions from those requiring immediate intervention and from testicular cancer.

TESTICULAR TORSION

What is a distinctive sign of testicular torsion?

Testicular torsion occurs in approximately one in 4,000 male individuals younger than 25 years of age each year [164]. In 90% of cases, intravaginal torsion is caused by a congenital malformation of the processus vaginalis [164]. Predisposing factors include increased testicular volume, testicles with horizontal lie, history of cryptorchidism, and a spermatic cord with a long intrascrotal portion [166]. Surgery to repair the torsion is necessary to save the testicle; thus, early diagnosis is critical [164; 165].

The most common misdiagnosis of testicular torsion is epididymitis [164; 167]. The first step should be to determine the onset of pain, as testicular torsion is associated with pain of sudden onset; in contrast, the onset of pain is insidious in epididymitis and other conditions [164; 165]. The physical examination also plays an important role in distinguishing testicular torsion from epididymitis. A key distinction is the absence of the cremasteric reflex in testicular torsion, which has been found to have a sensitivity of at least 99% in two studies of boys [167; 168]. To elicit this reflex, the medial thigh is stroked or pinched, which causes contraction of the cremaster muscle and elevation of the testis. If the testicle moves at least 0.5 cm, the reflex is positive [164]. Other distinguishing features include the area of tenderness, appearance of the scrotum, and testicular lie (***Table 9***) [164; 165; 167; 168].

If the diagnosis of testicular torsion is still in question after physical examination or if the onset of pain was 6 to 12 hours previously, color Doppler ultrasonography should be carried out [164; 165]. This imaging study has been found to have a sensitivity of 88% and a specificity of 90% in detecting testicular torsion in boys [169]. Decreased or absent blood flow and rotation of the spermatic cord on the affected side are indicators of testicular torsion [164; 166]. Scintigraphy with technetium 99m pertechnetate has a higher sensitivity, but this modality is not as readily available as ultrasonography in some institutions [164; 170].

A diagnosis of testicular torsion, whether highly suspected or definitive, requires immediate surgical intervention, and a surgical consultation should be obtained [164; 165]. The success rate for manual detorsion has been low (approximately 26%), so this procedure should be avoided as an alternative to surgical treatment [164; 171].

EPIDIDYMITIS

Inflammation of the epididymis affects a small proportion of men. Few epidemiologic studies are available, but the prevalence has been estimated to be approximately 0.29% to 0.9% and is the same across racial/ethnic populations [172]. Acute epididymitis is usually caused by bacterial infection, and the source of the infection varies. For men who are younger than 35 years of age and sexually active, the source is most commonly an STI. The most frequently identified micro-organisms are *C. trachomatis* and *Neisseria gonorrhoeae* [57; 173]. The diagnosis and treatment of epididymitis caused by STIs are discussed later in this course.

Among men who are older than 40 years of age, epididymitis is usually associated with bacterial infection of the urinary tract. Epididymitis has also been reported as a side effect of the drug amiodarone, used for ventricular arrhythmias [174]. A review of the literature indicated that the time to onset of the condition ranged from 4 to 71 months and developed at a daily dose of 200–800 mg [174; 175]. In many cases, there is no known etiology [176]. When pain, swelling, and/or inflammation persist for more than three months, the condition is considered to be chronic.

Men with acute epididymitis usually present with unilateral pain and tenderness in the testicle [173]. Additional symptoms include dysuria, urinary frequency or urgency, and symptoms related to the source of infection (e.g., fever, chills, or pain). Urinalysis and urine culture should be done to determine the presence of infection [175; 176].

Obtaining a careful history is an important first step in the diagnosis of epididymitis. The practitioner should ask about the sexual history; surgical history, especially in the scrotal area; the location, severity, and frequency of pain; and the presence and duration of symptoms [176]. When symptoms have been present for three months or longer, the Chronic Epididymitis Symptom Index can help determine the impact of symptoms on the quality of life [176].

As stated previously, several findings on physical examination can distinguish epididymitis from testicular torsion [164; 165; 167; 168]. The physical examination should also include evaluation of the abdomen, especially to check for tenderness in the flank and bladder distention, and the inguinal regions [165]. Examination of the scrotum should be carried out bilaterally, assessing the degree of swelling, presence of erythema, and differences in size [165].

Acute infectious epididymitis is treated by addressing the underlying infection, and antibiotics should be chosen according to the causal micro-organism. Symptomatic relief for both infectious and noninfectious epididymitis can be achieved with bed rest, scrotal support and elevation, ice packs, and anti-inflammatory agents or analgesics. If tenderness or swelling persists after treatment with antibiotics or if a mass becomes palpable, further evaluation should be carried out to rule out testicular cancer [173; 177]. Watchful waiting is suggested for chronic epididymitis [176].

Consultation with a urologist may be appropriate for men with complications or with chronic epididymitis [173]. Scrotal exploration may be necessary if abscess, testicular infarction, or pyocele develops. Epididymectomy has been used to treat chronic epididymitis, but the outcomes have varied widely [176].

VARICOCELE

A varicocele is a dilated, tortuous inflammation of the veins of the spermatic cord above the testicle. A prevailing thought has been that the superior mesenteric artery compresses the left renal vein over the aorta, also known as the "nutcracker effect" [178]. This theory has been confirmed by studies that have shown that varicoceles are less common in obese men [178; 179]. It has also been suggested that the condition is caused by damage to the contractile mechanism of the smooth muscle organization of spermatic veins [180]. As a result of anatomic differences, the condition is more common in the left testicle, but advances in imaging have led to reports of high rates of bilaterality [181]. Varicocele can cause discomfort in the scrotal area, but usually the condition is asymptomatic [165].

The frequency of varicocele among adolescents and young adults is approximately 15% to 20%, and the rate is higher among men who have some level of infertility, with reports of 77% and 81% in some studies [181; 182]. A study of older men (mean age: 60.7 years) demonstrated a prevalence of 42% [183].

Varicoceles vary in size, and large ones can be identified through physical examination alone. Varicoceles can have an adverse effect on spermatogenesis, and infertility has been associated with varicoceles that can be palpated [182]. The most significant finding is a feeling of a "bag of worms" when the scrotum is palpated [165; 182]. The varicocele may disappear or be substantially reduced when the patient is recumbent [182]. Smaller varicoceles can be detected by asking the patient to perform the Valsalva maneuver in the standing position [182]. In older men (at least 60 years of age), varicoceles have been associated with significantly smaller and soft testes [183]. Color Doppler ultrasonography is the diagnostic procedure of choice when the findings of the clinical examination are inconclusive [182].

The American Urology Association and the American Society for Reproductive Medicine recommend surgical varicocelectomy be considered in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men.

(https://www.auanet.org/guidelines/guidelines/male-infertility. Last accessed June 6, 2022.)

Strength of Recommendation/Level of Evidence: Moderate/B (Applies to most patients in most circumstances but better evidence could change confidence)

The treatment of varicocele depends on several factors, including the age of the patient, the size of the varicocele, the results of semen analyses, and the patient's desire for fertility [182]. Varicoceles in adolescents and young adults have been associated with significant loss of testicular volume and growth arrest of the testes, the risk of which increases with the size of the varicocele [184; 185]. These individuals should be monitored with physical examination and semen analyses to detect changes in testicular function, as earlier treatment will increase the likelihood of recovering normal spermatogenetic function [182; 186]. Advances in minimally invasive procedures and surgeries have led to significant strides in the management of symptomatic varicoceles [187]. Many experts agree that indications for surgical intervention in adolescents are pain, large varicoceles, hypotrophy of the

involved testicle, bilateral varicocele, intratesticular varicocele, and abnormal semen parameters on serial evaluation. The ideal method for treating adolescent varicocele has not been clearly established, but the main task is to decrease the number of recurrences and complications while retaining optimum testicular function. Because of this, many surgeons respect the attitude "catch-up growth" [188]. Treatment approaches and outcomes of therapy are discussed more fully in the section on infertility.

TESTICULAR CANCER

Testicular cancers are primarily germ cell tumors and are classified as seminomas and nonseminomas, the latter type being more clinically aggressive [177]. Testicular cancer is rare, accounting for 0.5% of all malignant tumors [177; 190]. However, the worldwide incidence of this type of cancer has been increasing in the past six decades [177]. As with other testicular conditions, this cancer is most common among male individuals 20 to 34 years of age [177; 189]. Early detection results in a cure rate of approximately 95% [177].

Prevalence

In 2019, there were an estimated 283,792 men living with testicular cancer in the United States [190]. In 2022, there will be an estimated 9,910 new cases of testicular cancer and 460 deaths. According to 2000–2019 SEER data, the incidence is highest among non-Hispanic White men (7.3 per 100,000), followed by American Indian/Alaska Native (10.6 per 100,000) and Hispanic men (5.9 per 100,000), Asian/Pacific Islander men (2.4 per 100,000), and Black men (1.5 per 100,000) [191].

Etiology

What is the primary risk factor for testicular cancer?

Among the several risk factors for testicular cancer, the primary one is cryptorchidism, which can increase the risk 11-fold [177]. Other risk factors include a family history of the disease, testicular dysgenesis, and Klinefelter syndrome [177]. A history of cancer in one testicle confers an increased risk (2% to 5%) of cancer in the contralateral testicle over the 25 years following diagnosis [192].

Screening

The USPSTF does not recommend routine screening for testicular cancer—by either clinician examination or self-examination—for asymptomatic adolescent and adult male individuals, as there is no evidence that screening reduces mortality [193]. The USPSTF notes that instead of screening, men should be advised to report testicular problems promptly, as cure rates are high for any stage of testicular cancer [193].

The European Association of Urology recommends high-frequency (i.e., >10 MHz) testicular ultrasound be used to confirm a testicular tumor even in the presence of a clinically evident testicular lesion.

(https://uroweb.org/guidelines/testicular-cancer. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Diagnosis

Testicular cancer usually presents as discomfort or swelling in the testicles that is suggestive of epididymitis or orchitis [177]. Physical examination will demonstrate a palpable mass [177]. Occasionally, the patient may note tender or swollen breasts or loss of sex drive.

According to the NCCN guideline for the treatment of testicular cancer, testicular ultrasonography is optional if a diagnosis is obvious from the physical examination, but the guideline notes that this diagnostic test is usually done to define the lesion [177]. Both the NCCN and ASCO recommend measuring serum levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (beta-hCG), and lactate dehydrogenase (LDH) to help determine if the testicular mass is a germ cell tumor and, if so, whether it is a seminoma or a nonseminoma [177; 194]. A nonseminoma is associated with an elevated AFP level; in contrast, an elevated level of beta-hCG, with a normal AFP level, usually indicates a seminoma [177]. Additional evaluation should include a chest x-ray and CT of the abdomen and pelvis to determine if lymph nodes are involved [177]. If metastatic disease is suspected, further imaging studies, such as bone scan, magnetic resonance imaging, or positron emission tomography, may be necessary. Open biopsy is not usually performed [177].

Treatment Options

Men with suspected testicular cancer should be referred to an oncologist who will discuss treatment options, which include orchiectomy and radiation therapy or chemotherapy, depending on the type of tumor and the stage of disease. Lymph node dissection may also be necessary for metastatic disease. The possibility of sperm banking should be discussed before any type of treatment is initiated [177].

Treatment options for early-stage seminoma (stage I, confined to the testicle and epididymis) are active surveillance (preferred), single-agent carboplatin (one or two cycles), or radiation therapy [177].

Radiation therapy is recommended for stage II seminoma (involvement of nearby lymph nodes), with the treated area extended to include the ipsilateral iliac lymph nodes [177]. If radiation is contraindicated, chemotherapy with three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP) is recommended. If chemotherapy is given, both regimens are recommended [177]. Chemotherapy with EP or BEP is recommended for stage III seminoma (involvement of distant lymph nodes and/or viscera) [177].

Treatment options for nonseminoma include surveillance, chemotherapy, and retroperitoneal lymph node dissection [177]. Selecting the appropriate therapy involves consideration of many factors, including the extent of disease in the lymph nodes, the levels of serum tumor markers before and during treatment, radiographic findings, and the commitment of the patient to adhere to surveillance protocols that involve frequent blood work and CT [177]. Chemotherapy involves either EP or BEP [177].

The cure rates for testicular cancer are high, even when cancer is at an advanced stage at the time of diagnosis [177]. The overall five-year survival for testicular cancer (all stages) is 95.2% [190].

Follow-Up

Men who have been treated for testicular cancer should be followed up at regular intervals to monitor for signs of recurrence. Follow-up visits typically include a history and physical examination and serum tumor markers. The ASCO guideline on the serum tumor markers for male individuals with germ cell tumors notes that there is insufficient evidence to determine whether monitoring tumor markers improves survival or health outcomes but nonetheless recommends measuring AFP and beta-hCG levels during each surveillance visit, and the NCCN also recommends an LDH as part of surveillance [194]. Evidence is also lacking regarding optimal surveillance intervals, and the intervals vary according to diagnosis (seminoma or nonseminoma) and stage of disease [177]. In general, the recommended intervals are every two months in the first year, every three months in the second year, every six months in the third and fourth years, and annually thereafter [177]. It is recommended that surveillance continue for at least 10 years [177; 194]. Chest x-ray and computed tomography of the abdomen and pelvis are recommended at greater intervals [177].

The follow-up evaluation plays an important role in assessing for the long-term effects of treatment. The primary effect of chemotherapy is oligospermia, but sperm production can be recovered [195; 196]. A population-based study found that 70% of testicular cancer survivors fathered children [197]. Secondary acute leukemias have been reported to develop after chemotherapy and radiation therapy, and other consequences of platinum-based chemotherapy include hearing deficits and impaired renal function [198; 199]. Melanomas and cancers at many sites have been associated with radiation therapy, occurring 10 years or more after treatment [198]. Lastly, the risk of cardiac events has been increased for testicular cancer survivors who had been treated with radiation therapy and/or chemotherapy [200].

MALE BREAST CANCER

What is the usual treatment approach for male breast cancer?

Breast cancer in men is rare; an estimated 2,710 new cases will be diagnosed in the United States in 2022, and an estimated 530 men will die of the disease [16]. These figures represent less than 1% of all breast cancer diagnosed in this country. Although the numbers are low, the prevalence has increased 26% since the early 1980s, prompting increased attention and highlighting the need to emphasize to men—and their healthcare providers—that breast cancer is not confined to women [201]. The lack of awareness of the disease has led to a longer time between the development of symptoms and diagnosis and to a later age (mean age: 67 years) and stage of disease at the time of diagnosis compared with women [201; 202].

Male breast cancer has not been extensively studied, and research is difficult because of the small numbers of men with the disease. Reviews of the literature have been helpful in identifying risk factors, clinical and pathologic characteristics, and the role of genetics [201; 202; 203]. Studies have shown that male breast cancer differs from female breast cancer in many ways. For example, some risk factors unique to men include the following [203]:

- Undescended testes
- Orchiectomy
- Infertility
- Gynecomastia
- Mastitis
- Breast trauma
- Infertility
- Klinefelter syndrome
- Radiation to the chest wall

BRCA2 mutation is found in approximately 4% to 16% of men with breast cancer [203].

A painless subareolar lump or swelling is the most common presenting symptom, occurring in approximately 85% of men with breast cancer [201; 204]. Other common symptoms are nipple retraction, localized pain, or nipple ulceration, bleeding, or discharge. About 1% to 2% of men will have no symptoms [201; 204]. In diagnosing male breast cancer, the primary consideration is to distinguish cancer from gynecomastia, which is present in about 30% of healthy men [202].

The approach to the diagnostic evaluation of male breast cancer is the same as for female breast cancer. A history and physical examination will help determine potential risk factors and identify the clinical features. Mammography has good sensitivity and specificity, and ultrasonography may be useful, especially for detecting involvement of the lymph nodes [202]. Biopsy is essential for elucidating the pathologic characteristics. In male breast cancers, the overexpression of estrogen receptor and progesterone receptors is likely [203; 205].

As noted, data on male breast cancer are limited, and recommendations for treatment have been extrapolated from the literature on female breast cancer and from small series of men with the disease. Modified radical mastectomy is used most often, with lumpectomy rarely performed [203]. Sentinel node biopsy has also been effective in men [206; 207]. Adjuvant radiation therapy has been associated with a lower local recurrence rate and a higher survival rate [202; 203]. Adjuvant chemotherapy has been carried out according to guidelines for women at high risk for recurrence. Adjuvant hormone therapy has a clear role in the treatment of men with hormone receptor-positive cancer, with reductions in recurrence and death [204; 208]. In addition, tamoxifen has led to a 50% response rate for metastatic breast cancer [202].

Five-year survival rates for men with breast cancer have been reported to be between 40% and 65% [201; 202]. In one retrospective study, the median survival was 87 months (83 months for men with invasive disease) [203]. Older age, higher stage of disease, and increasing tumor size have been associated with shorter survival [203]. The risk of second cancers (breast and nonbreast) appears to be high [209].

MALE SEXUAL HEALTH

Sexual dysfunction affects more than a quarter of men, yet attention to sexual health is low because of the lack of validated evidence-based guidelines for diagnosis and treatment as well as men's hesitancy to discuss sexual health issues with their primary healthcare providers [210; 211]. Clinicians should include questions about sexual function in routine health evaluations and foster an environment of trust and open dialogue to help elicit information on sexual health from their male patients.

Issues related to sexual health change over the course of a man's lifetime. Early ejaculation is of concern to men across the ages, erectile dysfunction and late-onset hypogonadism are of special concern to older men, and infertility and STIs are more common issues among younger men.

PREMATURE EJACULATION

The AUA definition of premature ejaculation is "poor ejaculatory control, associated bother, and ejaculation within about two minutes of initiation of penetrative sex that has been present since sexual debut" [354]. This definition and others have not been evidence based, however, and the International Society of Sexual Medicine charged a panel of experts with developing an evidence-based definition. According to this definition, premature ejaculation is "a male sexual dysfunction characterized by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy" [213]. The definition is limited to men with lifelong premature ejaculation and those for whom the condition is not caused by another physical, mental, or psychological health condition. Some have called for the condition to be called "early" ejaculation as a more accurate description of the condition [214].

Premature ejaculation is thought to be the most common sexual disorder among men, and the condition is associated with a high rate of psychosocial distress and has a substantial impact on men's relationships with their partners [215; 216].

Prevalence

The reported prevalence of premature ejaculation in the United States has varied widely, ranging from 5% to 40%, depending primarily on the definition [210; 212]. The highest prevalence is found among men who are 60 years of age or older [214].

Diagnosis

There are no established criteria for the diagnosis of premature ejaculation; clinicians should assess medical, relationship, and sexual history and perform a focused physical examination to make the diagnosis [354]. Laboratory studies or physiologic testing is needed only if the history or physical examination suggests a complex cause [212; 354]. Among the details to be elicited from the history are [212]:

- Frequency and duration of premature ejaculation
- Relationship of premature ejaculation to specific partners
- Degree of stimulus resulting in premature ejaculation
- Nature and frequency of sexual activity (foreplay, masturbation, intercourse, use of visual cues)
- Impact of premature ejaculation on sexual activity
- Types and quality of personal relationships and quality of life
- Aggravating or alleviating factors
- Relationship to drug use or misuse

AUA RECOMMENDED PHARMACOLOGIC THERAPY OPTIONS FOR PREMATURE EJACULATION		
Agent	**Daily Dose[a]**	**Pre-Intercourse Dose (On Demand)**
Nonselective serotonin reuptake inhibitor		
Clomipramine (Anafranil)	12.5–50 mg	25–50 mg (4 to 24 hours prior to sexual activity)
Selective serotonin reuptake inhibitors		
Fluoxetine (Prozac)	5–20 mg	—
Paroxetine (Paxil)	10 mg, 20 mg, or 40 mg	20 mg (3 to 4 hours prior to sexual activity)
Sertraline (Zoloft)	25–200 mg	50 mg (4 to 8 hours prior to sexual activity)
Topical agent		
Lidocaine/prilocaine cream (EMLA cream)	—	Lidocaine 2.5%/prilocaine 2.5% (20 to 30 minutes prior to sexual activity)
[a]The lowest dose should be used when beginning therapy, with upward titration based on response.		
Source: [212; 354]		*Table 10*

The patient's partner may be helpful in providing a description of the problem, and care should be taken to distinguish premature ejaculation from erectile dysfunction [212]. The AUA recommends that, for men with concomitant premature ejaculation and erectile dysfunction, erectile dysfunction should be treated first [212].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Male Training Center for Family Planning and Reproductive Health, asking men about problems with sexual function is particularly important to identify underlying cardiovascular disease among men who present with symptoms of sexual dysfunction routinely starting at 25 years of age. Specific questions include if the man is experiencing sexual dysfunction such as inability to obtain and maintain an adequate erection for satisfactory sexual activity (impotence, erectile dysfunction), premature or delayed ejaculation, loss of libido, painful intercourse, and also priapism, a prolonged painful erection not associated with sexual desire.

(https://rhntc.org/sites/default/files/resources/mtc_male_prevrhc_2014.pdf. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Treatment Options

The treatment approaches for premature ejaculation include psychologic, behavioral, and pharmacologic therapies, and the risks and benefits of all options should be discussed with the patient and, when possible, his partner [212; 354]. Behavioral therapy was once considered to be the standard therapy, but studies have shown that the best approach may involve a combination of therapies to address the limitations of each approach as well as the multimodal causes of premature ejaculation [210; 217; 218]. The 2022 AUA/Sexual Medicine Society of North America guideline recommends that, in addition to pharmacologic treatment, providers consider referring men with premature ejaculation to a mental health professional with expertise in sexual health [354].

No medication has been approved for the treatment of premature ejaculation, leaving the pharmacologic treatment to involve the off-label use of serotonin reuptake inhibitors or topical anesthetics that act by prolonging the latency of ejaculation [210; 212; 218; 219; 354]. The recommended first-line pharmacotherapeutic options are "on demand" clomipramine; a nonselective serotonin reuptake inhibitor; daily selective serotonin reuptake inhibitor (e.g., fluoxetine, paroxetine, sertraline); and topical penile anesthetics [212; 354]. The doses studied have varied, and dosing is prescribed as either continuous (daily regimen) or situational (taken only before sexual activity); the optimal duration of therapy has not been determined (***Table 10***) [212; 354]. The side effects of these drugs have not been evaluated outside the depression setting, but the effects appear to be similar for men who are not using the drug for depression, with the most common effects being nausea, dry mouth, and drowsiness [212].

Treatment with topical lidocaine/prilocaine has also been shown to be effective in increasing the latency of ejaculation and is another option recommended by the AUA [212; 220; 221]. The drug is typically applied 20 to 30 minutes before sexual activity; earlier application (30 to 45 minutes prior to sexual activity) has led to numbness of the penis and loss of erection in a substantial number of men [221]. Topical treatment avoids adverse events associated with systemic therapy [222]. In 2016, the European Union approved a topical eutectic lidocaine/prilocaine metered-dose spray (Fortacin) for use in the treatment of primary premature ejaculation [223; 224]. The spray has not been approved for this use in the United States [225].

One drug, dapoxetine, a short-acting selective serotonin reuptake inhibitor, is the first drug developed specifically for premature ejaculation, and it has been approved for use in several European countries, but not in the United States or Canada [222]. Several studies and systematic reviews have shown dapoxetine to substantially improve (compared with placebo) intravaginal ejaculatory latency time, perceived control, and patient-reported global impression of change and decrease related personal distress and difficulty [222; 226; 227; 228]. However, the agent is characterized by discontinuation rates of up to 90%, primarily due to side effects, cost issues, efficacy below expectations, and the need for scheduling sexual intercourse [224]. The most common side effects have been nausea, dizziness, diarrhea, insomnia, and headache.

Psychological and behavioral therapies are valuable components of treatment [210; 217; 218]. Relationship counseling and sex therapy can help facilitate communication between the patient and his partner and ease tension surrounding sexual activity. Psychologic and behavioral therapies should focus on gaining confidence, learning control techniques, lessening performance anxiety, overcoming barriers to intimacy, achieving pleasure, and gaining satisfaction [210; 217].

ERECTILE DYSFUNCTION

Erectile dysfunction can be conceptualized as an impairment in the arousal phase of sexual response and is defined by the AUA as "the consistent or recurrent inability to attain or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance" [355]. Erectile dysfunction is primarily a vascular disorder, but hormonal, neurologic, and psychologic factors are also involved. Approximately 70% of cases are organic and not of psychologic origin [229]. The term erectile dysfunction has come to replace "impotence" to more accurately describe a condition that is not associated with a loss of sexual desire or problems with ejaculation or orgasm [230].

Prevalence

Erectile dysfunction is estimated to affect 50 million men in the United States and more than 150 million men worldwide [231]. The prevalence has ranged from 10% to 30% among men 40 to 49 years of age and from 25% to 76% among men older than 70 years of age [232; 233; 234]. Ethnicity has also been a factor, with a higher rate for Black men and a lower rate for Hispanic men compared with White men [232]. However, another study showed that Hispanic men were more likely to report erectile dysfunction [234].

Erectile dysfunction has been reported to be more common among men with comorbidities; independent risk factors include age, diabetes, metabolic syndrome, cardiovascular disease, obesity, and sedentary lifestyle [214; 234; 235]. Among men with no known cardiovascular disease, erectile dysfunction has preceded coronary artery disease, stroke, and peripheral artery disease by an average of three years (range: two to five years) [236]. In addition, a meta-analysis (14 cohort studies; 92,757 men) showed that erectile dysfunction was an independent risk factor for cardiovascular and cerebrovascular events [237]. Other risk factors for erectile dysfunction include hormone disorders, neurologic conditions, psychologic disorders, history of surgery or radiation in the pelvic region, use of illicit drugs, and some prescription drugs (most notably, antihypertension agents) [238]. Encouraging men with these risk factors to modify their lifestyle and/or treating comorbidities may help reduce the risk of erectile dysfunction [239].

Diagnosis

A detailed medical history is integral to diagnosing erectile dysfunction, as the history may elucidate an underlying cause. It is important to also document a psychosocial and sexual history to evaluate the potential of other related or contributing factors [230]. The physical examination should involve assessment of the abdomen, genitals, and pulses in the lower extremity [230]. Validated questionnaires are recommended to assess the severity of erectile dysfunction, to measure treatment effectiveness, and to guide future management [355]. A morning serum total testosterone should be measured routinely; selected laboratory studies to consider are fasting glucose and serum lipid profile, hemoglobin A1c, and thyroid function tests [355].

Treatment Options

For whom is treatment with a phosphodiesterase-5 inhibitor contraindicated?

Erectile dysfunction is best managed with a combination approach [235]. Because of the strong relationship between erectile dysfunction and modifiable risk factors, lifestyle changes should be a first-line approach to managing the condition. The importance of achieving or maintaining a healthy body mass index, increasing exercise, and smoking cessation should be emphasized, especially given the relationship between erectile dysfunction and cardiovascular disease.

After treatment of erectile dysfunction is initiated, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate therapies into a sexual relationship [355]. Both the AUA and the ACP recommend oral phosphodiesterase-5 inhibitors as first-line pharmacotherapy for erectile dysfunction in men for whom this class of drugs is not contraindicated [230; 231; 355]. Four drugs in the class have been approved for use in the treatment of erectile dysfunction: sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra, Spedra). Sildenafil and vardenafil differ from tadalafil with respect to the time to maximum serum level (1 hour vs. 2 hours) and serum half-life (4 hours vs. 18 hours) [230]. Furthermore, the duration of action is longest for tadalafil (up to 36 hours) [240]. The inhibitory effect of these drugs causes vascular smooth muscle relaxation in the corpus cavernosum, resulting in increased erection hardness and prolonged duration in men with erectile dysfunction who have sufficient intact vasculature [355].

Data from multiple trials and systematic reviews have demonstrated similar efficacy for phosphodiesterase-5 inhibitors in treating erectile dysfunction, particularly for sildenafil, tadalafil, and vardenafil [355]. Each of these drugs substantially improves erectile function and successful sexual intercourse compared with placebo [231]. Relative efficacy is less clear for avanafil because published comparative studies are limited. The ACP notes that there is insufficient evidence for recommending one drug over another and suggests that the choice be made according to the preferences of an individual patient with respect to ease of use, cost, and the adverse effects profile [231]. One systematic review and meta-analysis found evidence that tadalafil is the most effective agent, followed by vardenafil, with no major differences in the safety profile of any of the phosphodiesterase-5 inhibitors [241].

The side effects of all four drugs are similar, with headache, dyspepsia, facial flushing, nasal congestion, and visual disturbances being the most common events [230; 240; 242]. The FDA has issued two mandates to revise labeling of these agents. In 2005, the agency required labels for sildenafil, tadalafil, and vardenafil to reflect the possibility of sudden vision loss after taking the drugs for a period of time [243]. The alert was associated with several case reports suggesting a temporal association between use of one of the drugs and nonarteritic anterior ischemic optical neuropathy (NAION), a rare disorder characterized by sudden loss of vision in one eye [243; 355]. However, subsequent studies showed that the risk of NAION was similar among men who were and were not taking a phosphodiesterase-5 inhibitor [244; 245]. Risk factors for spontaneous NAION include older age, White race, small optic discs with low cup-to-disc ratio, and vascular disease, leading some investigators to suggest an examination of the fundus be performed on men who may be at higher risk for NAION before a phosphodiesterase-5 inhibitor is prescribed [243].

In 2007, the FDA mandated changes to the labels of phosphodiasterase-5 inhibitors to more prominently display warnings about the potential for sudden hearing loss [246]. A cross-sectional population-based study of more than 11,000 men subsequently demonstrated a higher likelihood of self-reported hearing loss associated with use of any phosphodiasterase-5 inhibitor (odds ratio: 2.23), but the association was significant only for sildenafil [247].

Use of a phosphodiesterase-5 inhibitor is contraindicated in several situations. They should not be taken by men who take organic nitrates (nitroglycerin) or nitrites (amyl nitrite) [248; 249]. Vardenafil should not be used for men with a history of prolonged QT interval (or who take medication to prolong the QT interval) [230]. The use of a phosphodiesterase-5 inhibitor concomitantly with an alpha-blocker for lower urinary tract symptoms may lead to increased systemic vasodilation and hypotension [230].

Men who are being treated with a phosphodiesterase-5 inhibitor should be followed up closely to monitor efficacy and side effects. Attention to changes in health status and other medications is essential to avoid drug interactions. Clinicians should emphasize the importance of men providing information about treatment with a phosphodiesterase-5 inhibitor in case of a cardiovascular emergency [230].

Although the initial treatment option preferred by most men with erectile dysfunction is a phosphodiesterase-5 inhibiter, the AUA Panel notes that it is valid for men to begin with any type of established treatment, and recommends that patients be informed of all treatment options that are not medically contraindicated. The AUA guideline provides data on success rates, patient and partner satisfaction rates, and potential adverse effects for the following treatment options [355]:

- Vacuum erection device: An effective, low-cost option with high rates of patient and partner satisfaction. May have a role as "rescue device" or adjunct to pharmacologic therapy.
- Intraurethral alprostadil: Involves insertion of a delivery catheter into the urethral meatus and depositing an alprostadil tablet in the urethra; requires an in-office trial to insure effectiveness and safety. Variable rates of success (30% to 78%).
- Intracavernosal injection: Administered by injecting medication (i.e. alprostadil) into the corpus cavernosa of the penis to produce an erection; an in-office injection test should be performed. Reported success rates range from 58% to 100%.

- Penile prosthesis implantation: Surgical procedure that requires thorough patient and partner counselling. Available devices include malleable (non-inflatable) models as well as inflatable prostheses. Satisfaction rates vary across models, ranging from 66% to 88%.

Intracavernosal injection of a vasoactive drug is associated with the highest potential for priapism, and clinicians should ensure that men understand the correct technique and the importance of seeking medical intervention for a prolonged erection [230]. Only vacuum erection devices with a limiter (a feature that limits the amount of vacuum pressure and reduces potential for penile injury) should be recommended, whether purchased over the counter or procured by prescription [230; 355]. The AUA advises that for men with erectile dysfunction, low-intensity extracorporeal shock wave therapy and intracavernosal stem cell therapy are considered investigational treatment options [355]. The risks associated with penile prostheses include mechanical failure, erosion, and infection [230]. The AUA guideline does not recommend the use of trazodone, testosterone therapy (for men with normal serum levels), or yohimbine and other herbal therapies [230].

Psychosocial therapy is an important component of treatment for erectile dysfunction. A meta-analysis showed that group psychotherapy in combination with sildenafil significantly improved erectile function and successful sexual intercourse compared with sildenafil alone [250].

LATE-ONSET HYPOGONADISM

In both men and women, levels of sex hormones decline with age. However, the ways in which these levels change and the symptoms associated with the decline differ greatly between men and women. There is no well-defined equivalent of menopause in men, although the phrase "andropause" is used frequently to refer to decreased testosterone and resulting symptoms. Other phrases, most notably androgen deficiency syndrome and late-onset hypogonadism, may be more accurate descriptors of the process. By any name, the condition is a complex of symptoms that includes loss of sexual satisfaction and overall well-being [251]. The condition is related to lower testosterone levels, which begin to decrease 1% to 2% each year beginning at 30 years of age [252].

Late-onset hypogonadism is distinct from hypogonadism in younger male individuals. For boys and young men, hypogonadism is related to testicular failure and is usually associated with a congenital abnormality, most often Klinefelter syndrome [251]. In older men with hypogonadism, testosterone levels are rarely as low as the levels in young men with primary hypogonadism [251].

Several important questions about late-onset hypogonadism remain unanswered [252; 253]:

- It is unclear whether the symptoms are caused by a reduction in testosterone or are a result of the normal physiologic process of aging.
- There is no consistent level of testosterone to define hypogonadism, and there is confusion about what testosterone levels should be measured.
- There is ongoing debate about the risk-benefit ratio of testosterone therapy for older men.

Prevalence

There is a wide range in the reported prevalence of late-onset hypogonadism. In a population-based observational study, symptomatic androgen deficiency was found in nearly 6% of men 30 to 79 years of age, whereas in the Hypogonadism in Males (HIM) study, the prevalence was nearly 39% among men 45 years of age and older visiting primary care practices [254; 255]. The prevalence increases substantially with age and is similar across racial/ethnic populations [254; 255].

Diagnosis

A diagnosis of late-onset hypogonadism requires both documentation of relevant symptoms and measurement of testosterone levels. The condition is associated with a variety of physiologic, psychologic, cognitive, and sexual symptoms; some signs and symptoms are more specific than others, and no combination of symptoms is typical (***Table 11***) [252; 255].

Diagnosing late-onset hypogonadism (testosterone deficiency) is challenging because many signs and symptoms are associated with the normal process of aging or can be attributed to coexisting conditions. Two questionnaires that can help to identify late-onset hypogonadism are the Androgen Deficiency in Aging Males (ADAM) questionnaire and the Aging Males' Symptoms (AMS) scale [256; 257; 258; 259; 260]. The ADAM questionnaire consists of 10 questions, and the condition is defined by a positive response to two specific questions: "Do you have a decrease in libido (sex drive)?" and "Are your erections less strong?" or to any three of the other questions [256]. The AMS scale asks men to provide a score of 1 to 5 to each of 17 somatic, psychologic, and sexual symptoms. The ADAM questionnaire has been validated against testosterone levels, whereas the AMS scale was designed to evaluate the quality of life and has not been correlated to testosterone levels [261]. Both have excellent specificity but poor sensitivity [251].

SYMPTOMS AND SIGNS SUGGESTIVE OF TESTOSTERONE DEFICIENCY IN MEN	
Specific	Incomplete or delayed sexual development, eunuchoidism Loss of body (axillary and pubic) hair, reduced shaving Very small (especially <5 mL) or shrinking testes
Suggestive	Reduced sexual desire (libido) and activity Decreased spontaneous erections Breast discomfort, gynecomastia Inability to father children, low or zero sperm count Height loss, low trauma fracture, low bone mineral density Hot flushes, sweats
Nonspecific	Decreased energy, motivation, initiative, and self-confidence Feelings of sadness or being "blue," depressed mood, dysthymia Poor concentration and memory Sleep disturbance, increased sleepiness Mild unexplained anemia (normochromic, normocytic, in the female range) Reduced muscle bulk and strength Increased body fat, body mass index

Source: Modified, with permission, from Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018;103(5):1715-1744. *Table 11*

POTENTIAL BENEFITS AND RISKS OF TESTOSTERONE THERAPY	
Benefits	**Potential Risks**
Improvement in sexual desire and function	Stimulation of growth of prostate cancer
Increase in bone mineral density	Worsening of symptoms related to benign prostatic hypertrophy
Improvements in mood, energy, and quality of life	Liver toxicity and liver tumor
Change in body composition and improvement in muscle mass and strength	Gynecomastia
Improvement in cognitive function	Erythrocytosis Testicular atrophy and infertility Skin diseases Sleep apnea

Source: [262] *Table 12*

In its updated practice guidelines on the treatment of androgen deficiency, the Endocrine Society recommends making a diagnosis of hypogonadism "in men with symptoms and signs of testosterone deficiency and unequivocally and consistently low serum testosterone and/or free testosterone concentrations (when indicated)" [252]. Serum testosterone level fluctuates in relation to time of day and food intake; peak concentrations occur during the morning hours. Therefore, clinicians should measure total testosterone concentrations on two separate mornings while the patient is fasting [252]. Measured levels should be interpreted with caution as not all laboratories use total testosterone assays harmonized to the national standard [355]. Intercurrent acute illness, nutritional deficiency, and certain medications (e.g., opioids, glucocorticoids) can alter the expected serum testosterone concentration. In general, a total testosterone concentration of 300 ng/dL is the cut-off level below which testosterone replacement therapy is considered for most men with suspected late-onset hypogonadism.

Treatment Options

According to the Endocrine Society, how frequently should men receiving testosterone therapy by monitored?

The increase in treatment with testosterone has been tremendous. Although there are benefits of testosterone therapy, there are also many potential risks (***Table 12***), and the risk-benefit ratio for men with late-onset hypogonadism has not been clearly defined [255; 256; 261]. Because of questions about the benefits and harms of testosterone, the Endocrine Society is specific in its recommendations for testosterone therapy (***Table 13***) and recommends against a general policy of offering testosterone therapy to all older men with low testosterone levels [252].

RECOMMENDATIONS OF THE ENDOCRINE SOCIETY REGARDING TESTOSTERONE THERAPY FOR ADULT MEN WITH HYPOGONADISM	
Diagnosis and evaluation	*Recommendations* Make a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone deficiency and unequivocally and consistently low serum testosterone levels and/or free testosterone concentrations (when indicated). Confirm diagnosis by repeating measurement of fasting morning total testosterone. Measure serum luteinizing hormone and follicle-stimulating hormone levels to distinguish between primary (testicular) and secondary (pituitary-hypothalamic) hypogonadism. *Suggestions* Perform further evaluation to identify the etiology of hypothalamic, pituitary, and/or testicular dysfunction in men with hypogonadism. Measure serum testosterone level in men who have specific clinical signs and symptoms and consider measuring serum testosterone level in men who report less specific signs and symptoms. Measure morning total testosterone level by a reliable assay as the initial diagnostic test. Measure free or bioavailable testosterone level, using an accurate and reliable assay, in men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of sex hormone-binding globulin are suspected. Do not evaluate androgen deficiency during an acute or subacute illness. Measure bone mineral density with use of dual-energy x-ray absorptiometry scanning in men with severe androgen deficiency or low trauma fracture.
Treatment	*Recommendations* Use testosterone therapy for men with hypogonadism to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. Do not use testosterone therapy for men planning fertility in the near term or in men with breast or prostate cancer. Do not use testosterone therapy without further urologic evaluation in men with palpable prostate nodule or induration or a prostate-specific antigen (PSA) level of 3 or 4 ng/mL in men at high risk of prostate cancer (e.g., Black race, first-degree relative with prostate cancer). Do not use testosterone therapy for men with a hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, or uncontrolled or poorly controlled heart failure, or in men with type 2 diabetes (as a means of glycemic control) who have low testosterone concentrations. *Suggestions* Initiate testosterone therapy with any of the following regimens, chosen on the basis of an individual man's preference, consideration of pharmacokinetics, treatment burden, and cost: • Testosterone enanthate or cypionate: 75–100 mg IM weekly, or 150–200 mg IM every two weeks • Testosterone patch (nongenital): 5 mg, one or two applied nightly over the skin of the back, thigh, or upper arm (away from pressure areas) • Testosterone gel (1%): 5–10 g applied daily over a covered area of nongenital skin • Testosterone bioadhesive buccal tablet: 30 mg applied to buccal mucosa every 12 hours • Testosterone pellets: SC every three to six months (dose and regimen vary with the formulation used) • Oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets, where available Consider short-term testosterone therapy in men with HIV, low testosterone concentrations, and weight loss (when other causes of weight loss have been excluded) to induce and maintain body weight and lean mass gain. Do not routinely prescribe testosterone therapy to all men 65 years of age or older with low testosterone concentrations. Offer testosterone therapy on an individualized basis after discussing the risks/benefits with the patient.
Monitoring	*Recommendations* Evaluate the patient three to six months after the initiation of treatment and then annually. Determine hematocrit at baseline, at three to six months, and then annually. (Stop therapy if the hematocrit is higher than 54%.) Evaluate the patient for signs and symptoms of formulation-specific adverse events at each visit. Obtain a urologic consultation if there is any of the following: • Increase in serum or plasma PSA level >1.4 ng/mL within any 12-month period of testosterone treatment • PSA velocity >0.4 ng/mL/yr using the PSA level after 6 months of testosterone therapy as the reference (PSA velocity should be used only if there are longitudinal PSA data for more than two years.) • Detection of a prostatic abnormality on digital rectal examination • AUA/IPSS score >19 *Suggestions* Monitor testosterone levels three to six months after initiation of testosterone therapy, with an aim of achieving serum testosterone levels during treatment in the mid-normal range. (For men receiving testosterone enanthate or cypionate, the aim should be a testosterone level between 350 and 600 ng/dL at one week after the injection.) Repeat bone mineral density of the lumbar spine, femoral neck, and hip after one to two years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture.
Screening	*Recommendation* Do not screen for hypogonadism in the general population.

Source: [252] *Table 13*

Testosterone replacement is available in several forms, including oral agents, injectable formulations, transdermal gels and patches, and buccal tablets [252; 263]. In general, a decision on the type of therapy should be made according to the patient's preference, with consideration of several factors, including pharmacokinetics, cost, ease of use, and side effect profile [252; 263].

Follow-Up

Close follow-up is essential for men being treated with testosterone replacement. The clinical response and side effects should be monitored at intervals of three to six months [252]. The treatment target should be a testosterone level in the middle of the normal range [252]. Follow-up should include evaluation of the prostate, through determination of PSA levels and DRE at three to six months for men 40 years of age and older who have a baseline PSA greater than 0.6 ng/mL. In addition, a hematocrit level should be determined at three to six months and then annually; treatment should be discontinued if the hematocrit is greater than 54%.

MALE INFERTILITY

Infertility is clinically defined as the inability to conceive after one year of unprotected intercourse [264]. Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is the only cause in approximately 20% of infertile couples and is a contributing factor in another 20% to 40% [264]. Fertility declines with age, and research has shown that men older than 35 years of age are twice as likely to be infertile as men younger than 25 years of age [265; 266]. Approximately 15% of infertile men have azoospermia, the complete absence of sperm in the ejaculate [267].

Etiology

What proportion of male infertility or subfertility is potentially correctable?

More than half of male infertility or subfertility is potentially correctable; often, the cause is unknown. The causes, both correctable and uncorrectable, include [264; 268]:

- Varicocele
- Obstruction of a duct (epididymal, vasal, or ejaculatory)
- Ejaculatory dysfunction
- Testicular atrophy
- Hypogonadotropic hypogonadism
- Infection
- Side effects of medication
- Environmental toxins
- Bilateral cryptorchidism
- Genetic abnormality (Y chromosome microdeletion)
- Congenital absence of vas deferens

Diagnosis

According to the AUA guidelines, evaluation of suspected male infertility should include a complete medical and reproductive history, physical examination, and one or more semen analyses [264; 356]. Men with one or more abnormal semen parameters or presumed male infertility should be evaluated by a male reproductive expert. It is important not to rely solely on semen analysis, as an underlying medical or genetic cause of infertility may be missed [268]. Other tests may be necessary, depending on the findings of this initial evaluation. Clinicians should obtain hormonal evaluation including follicle-stimulating hormone (FSH) and serum testosterone for infertile men with any of the following: impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical examination [356].

The medical history can help to detect an underlying cause of infertility. Factors that can affect fertility include [268]:

- Kallmann, Young, or Kartagener syndrome
- Pituitary disease
- Previous testicular disorders
- History of inguinal, scrotal, or retroperitoneal surgery
- Anticancer chemotherapy

The reproductive history should address the following issues: frequency and timing of intercourse, duration of fertility effort, use of lubricants, and sexual history (including STIs) [264; 267; 268].

Physical examination may identify a varicocele, the most common cause of male infertility [165; 182]. Other findings on physical examination that may suggest a cause of infertility include small testes (less than 4 cm in greatest dimension or less than 20 cm3), signs of ductal obstruction (induration or engorgement of the vas deferens or epididymis), and abnormal distribution of hair and fat, which may indicate endocrinopathy [268].

As noted, the semen analysis should be carried out on at least two specimens, obtained at least one month apart [264]. The specimens should be collected after two to three days of abstinence. The World Health Organization (WHO) first established reference values for semen analysis in 1987 and published its sixth update in 2021 [269]. The 2020 AUA guideline references the 2010 WHO semen parameters and lower reference limit criteria for male infertility [356]:

- Semen volume: 1.5 mL
- Total sperm number: 39 million/ejaculate
- Sperm concentration: 15 million/mL
- Vitality: 58% live
- Total motility (progressive + nonprogressive): 40%
- Morphologically normal forms: 4.0%

Initially, the updated criteria met with controversy, with some noting that the new reference values would lead to fewer men being classified as infertile based on semen analysis alone [271; 272; 356]. No single abnormality among sperm parameters is diagnostic of infertility; the odds ratio for infertility increases with the number of abnormal semen parameters, rising sharply with two or more abnormal parameters [356].

Treatment Options

Treatment options are available for correctable causes of infertility. Varicoceles can be repaired through open or laparoscopic surgery or by percutaneous embolization [182]. Surgical treatment leads to elimination of the varicocele in 90% of men, with improvement in the semen quality, production of testosterone, and rates of subsequent pregnancy [182; 273]. For men with infertility related to obstruction, microsurgical reconstruction of the obstructed duct has led to the appearance of sperm in the ejaculate and higher rates of subsequent pregnancy [267]. Several techniques for retrieving sperm are also available. Options for reproductive assistance and adoption should be explored for men who have uncorrectable infertility. Genetic counseling should be offered to men with nonobstructive azoospermia due to primary testicular failure [267].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The National Collaborating Centre for Women's and Children's Health recommends that men be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility.

(https://www.nice.org.uk/guidance/cg156. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

SEXUALLY TRANSMITTED INFECTIONS

STIs are a serious public health concern. There are an estimated 26 million new infections annually and 68 million total STIs in the United States, of which youth 15 to 24 years of age account for about half [357]. In addition to the substantial morbidity associated with STIs, the financial cost is tremendous; nearly $16 billion in direct medical costs annually are associated with the eight major STIs (chlamydia, gonorrhea, hepatitis B virus, HIV, human papillomavirus [HPV], herpes simplex virus type 2 [HSV-2], trichomoniasis, and syphilis) [275]. The large majority of costs are attributable to HIV ($13.7 billion), followed by chlamydia ($691 million), gonorrhea ($271 million), and HSV-2 ($91 million) [57].

The discussion here is confined to STIs having the greatest impact on men: chlamydia, gonorrhea, syphilis, HSV-2, and HPV [57]. Although HSV-2 and HPV infections are more common among women than men, the infections have serious implications for men. For example, nearly one-third of the 22,000 HPV-associated cancers that occur each year in the United States develop in men [276]. Infection with HSV-2 increases the risk for HIV, which is particularly important for Black men, who are at greater risk for both HSV-2 and HIV [277].

Despite the availability of comprehensive guidelines for the testing and treatment of STIs, studies have shown poor compliance; in one study, fewer than one-third of individuals with an STI seen in an emergency department received recommended antibiotic treatment, and compliance with history-taking, diagnostic testing, and counseling ranged from 14% to 79% [278]. In addition, improvements in rates of HPV vaccination are needed [279].

Prevalence of STIs

The prevalence of STIs according to gender vary with infection; chlamydia, HSV-2, and HPV occur more often among female than male individuals; gonorrhea occurs at similar rates among female and male individuals; and syphilis occurs more often among male than female individuals [57; 277; 280]. Overall, almost two-thirds of all STIs occur in individuals 15 to 24 years of age [57]. Among men, most STIs are far more prevalent in the non-Hispanic Black population than in other ethnic/racial populations and are least prevalent in the Asian population (***Table 14***) [57; 277; 281].

Chlamydia

More than 1.5 million cases of chlamydia were reported to the CDC in 2020 [57]. The 2020 rate of chlamydia infection (481.3 cases per 100,000) represents a decrease of 13% over the rate in 2019. During 2019–2020, rates of reported chlamydia decreased among both men and women. Chlamydial infection occurs more than twice as commonly in women than men, and rates are highest among adolescents and young adults.

Gonorrhea

In 2020, a total of 677,769 cases of gonorrhea were reported to the CDC, making it the second most commonly reported notifiable sexually transmitted disease in the United States [57]. Rates of gonorrhea have increased 111% since the historic low of 98.1 cases per 100,000 in 2009. In 2020, the rate of gonorrhea among men was 236.3 cases per 100,000, compared with 150 cases per 100,000 among women [57].

RATE OF COMMON SEXUALLY TRANSMITTED INFECTIONS (STIs) AMONG MEN ACCORDING TO RACE/ETHNICITY, 2020							
STI	Prevalence (per 100,000)						
	All Men	Black (Non-Hispanic)	American Indian/ Alaskan Native	Hispanic	White (Non-Hispanic)	Asian	Native Hawaiian/ Other Pacific Islander
Chlamydia	336.7	883.7	315.8	198.0	113.2	72.0	300.6
Gonorrhea	236.3	819.5	272.3	144.8	77.4	46.6	195.8
Syphilis (primary and secondary)	20.7	57.7	32.6	23.4	11.0	8.9	30.7
Source: [57]							*Table 14*

Syphilis

In 2000–2001, the rate of syphilis (primary and secondary) was 2.1 cases per 100,000; however, the rate has increased almost every year since that time, increasing 6.8% between 2019 and 2020 [57]. In 2020, 133,945 cases of syphilis were reported, including 41,655 cases of primary and secondary syphilis, the most infectious stages of the disease. Rates of syphilis have increased in most racial/ethnic groups, with greatest increases among non-Hispanic American Indian/ Alaska Native persons and non-Hispanic persons of multiple races [57]. Young men who have sex with men are disproportionally impacted, accounting for a majority (53%) of all male syphilis cases in 2020 [57].

HSV-2

Genital herpes is a chronic, lifelong viral infection; the prevalence is unknown as the majority of persons infected have not had the condition diagnosed. Many individuals with HSV-2 have mild symptoms or unrecognized infection but shed the virus intermittently in the urogenital area. Consequently, most genital infections are transmitted by persons unaware that they have the infection. Most cases of recurrent genital herpes are caused by HSV-2, and 11.9% of persons 14 to 49 years of age in the United States are estimated to have acquired this infection [173]. In 2020, the CDC estimated the prevalence of HSV-2 at 18.6 million persons, though the actual number is likely to be considerably higher [57; 173]. The seroprevalence of HSV-2 is more than twice as high among female individuals (about 34%) than among male individuals (about 15%) [57]. As with other STIs, HSV-2 infection is more common among non-Hispanic Black men than other racial/ethnic populations [57].

HPV

Data on HPV infection in men are limited. According to a data brief published by the National Center for Health Statistics (NCHS), during 2011–2014, the seroprevalence of any HPV was 7.3% among adults 18 to 69 years of age, with 11.5% among men and 3.3% among women [282]. In the HIM study, an ongoing prospective cohort study of the natural history of HPV in men (from the United States, Mexico, and Brazil), the overall prevalence of HPV infection was 65.2%, with the highest rates among White and Black men (71.5% and 66.2%, respectively) and the lowest, among Asian/Pacific Islander men (42.2%) [281; 283]. An estimated 34,800 new HPV-attributable cancers occurred every year during 2012–2016; before introduction of HPV vaccines, approximately 355,000 new cases of anogenital warts occurred every year [173].

Prevention, Control, and Screening

Prevention and control are keys to lowering the prevalence of STIs, and the primary preventive strategies are: risk assessment, education, and counseling; limiting the number of sexual partners; abstinence or the use of condoms and barriers; and, in the case of HPV, with vaccination [173; 276]. The importance of abstaining from sexual activity should be emphasized to individuals with a confirmed STI [173].

Control of STIs involves the identification of asymptomatic individuals and of symptomatic individuals who may not seek health care; effective diagnosis and treatment; and the evaluation, treatment, and counseling of sex partners of infected individuals [173]. The CDC encourages clinicians to promote prevention with patient-centered education that focuses on risk reduction measures directed at an individual patient's personal risk [173]. Obtaining a thorough sexual history is an essential component of prevention, and the CDC suggests asking questions related to [173]:

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS FOR SCREENING FOR SEXUALLY TRANSMITTED INFECTIONS (STIs) IN MALE INDIVIDUALS	
STI	**Recommendation**
Chlamydia and gonorrhea	Insufficient evidence to recommend for or against screening in men
Syphilis	Strongly recommend screening for individuals at increased risk
Genital herpes	No screening for asymptomatic adults and adolescents
Source: [284; 360; 361]	*Table 15*

- Partners (gender and number)
- Protection (from STIs)
- Practices (types of sexual activity)
- Past history of STIs (patient and partners)
- Prevention (of pregnancy)
- Use of injected drugs (patient and partners)
- Exchange of money for sex (patient and partners)
- Other sexual practices

Practical strategies for risk assessment and counseling are provided in the CDC treatment guidelines document [173]. Healthcare providers should use simple, direct language when asking these questions, taking care to exhibit respect, compassion, and a nonjudgmental attitude [173]. Organizations such as the National Network of STI/HIV Prevention Training Centers, a CDC-funded group, can help providers enhance skills in counseling individuals about prevention. Resources can be found on the organization's website, available at https://www.cdc.gov/std/treatment/resources.htm.

The U.S. Preventive Services Task Force recommends behavioral counseling for all sexually active adolescents and for adults who are at increased risk for sexually transmitted infections.

(https://jamanetwork.com/journals/jama/fullarticle/2769474. Last accessed June 6, 2022.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

Recommendations for screening vary according to risk and the type of STI (***Table 15***) [284]. The USPSTF also recommends high-intensity behavioral counseling for all sexually active adolescents and for adults at increased risk for STIs and HIV [284]. The USPSTF has not issued recommendations for screening for HPV, but beginning in 2011, the Advisory Committee on Immunization Practices (ACIP) recommended HPV vaccination for male individuals [276]. The ACIP recommends routine use of quadrivalent HPV vaccine for boys 11 or 12 years of age and for male individuals 13 to 26 years of age who have not initiated or completed the three-dose series [276; 286]. The ACIP also notes that men 27 to 45 years of age may also be vaccinated if at high risk, as determined through shared decision-making [276; 285; 286]. In addition, hepatitis B vaccination is recommended for any patient who is being evaluated for an STI [173].

Diagnosis

The symptoms of STIs vary and are often similar to symptoms associated with other conditions of the urogenital tract, and some infected individuals may be asymptomatic.

Infection with chlamydia is often asymptomatic [173]. Diagnosis can be made by testing of a urethral or rectal swab or a urine specimen [173]. Nucleic acid amplification tests are the most sensitive tests and can be used for urine specimens [173].

Primary syphilis usually presents as a solitary chancre that develops at the site of infection approximately three weeks after exposure to the spirochete *Treponema pallidum* [287]. The chancre is typically painless and must be distinguished from other genital lesions, such as genital herpes, venereal warts, chancroid, and lymphogranuloma venereum (caused by *C. trachomatis*) [287].

Dark-field microscopy to detect *T. pallidum* is the optimum method of diagnosing syphilis. Although no such detection tests are commercially available, some laboratories provide locally developed and validated polymerized chain reaction (PCR) tests for the detection of *T. pallidum* [173]. A presumptive diagnosis of syphilis can be made with two types of serologic tests: nontreponemal tests (Venereal Disease Research Laboratory [VDRL] and rapid plasma regain [RPR] tests) and treponemal tests (such as fluorescent treponemal antibody absorbed [FTA-ABS] tests or the *T. pallidum* passive particle agglutination [TP-PA] assay) [173]. The CDC notes that using only one type of serologic test is insufficient for a diagnosis [173].

TREATMENT OF CHLAMYDIA, SYPHILIS, AND GONORRHEA AS RECOMMENDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION		
Infection	**Recommended Treatment**	**Notes**
Chlamydia	Doxycycline 100 mg orally twice daily for 7 days ALTERNATIVE REGIMENS Azithromycin 1 g orally in a single dose OR Levofloxacin 500 mg orally once daily for 7 days	A meta-analysis showed treatment failure among men was higher for azithromycin than for doxycycline.
Gonorrhea	Ceftriaxone 500 mg IM (single dose) PLUS Doxycycline 100 mg PO twice daily for seven days, unless chlamydia infection has been excluded	For persons weighing >150 kg, 1 g ceftriaxone should be administered. See guideline for alternative cephalosporin selection and dosing if ceftriaxone is not available.
Primary and secondary syphilis	Benzathine penicillin G 2.4 million units IM (single dose)	Additional doses do not enhance efficacy. For patients allergic to penicillin, alternative regimens include doxycycline (100 mg PO, twice daily for 14 days) or tetracycline (500 mg PO, four times daily for 14 days)
Source: [173]		*Table 16*

TREATMENT OF HSV-2 AS RECOMMENDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION			
Drug	**Treatment Dosage**		
	Initial Infection	**Episodic Recurrent Infection**	**Long-Term Suppression**
Acyclovir	400 mg three times daily for 7 to 10 days OR 200 mg, five times daily for 7 to 10 days	800 mg two times daily for 5 days OR 800 mg three times daily for 2 days	400 mg twice daily
Famciclovir	250 mg, three times daily for 7 to 10 days	125 mg two times daily for 5 days OR 1.0 g two times (single day)	250 mg twice daily
Valacyclovir	1 g two times daily for 7 to 10 days	500 mg two times daily for 3 days OR 1.0 g once daily for 5 days	500–1,000 mg once daily
Source: [173]			*Table 17*

Gonococcal infection, which is caused by *Neisseria gonorrhoeae* (a gram-negative diplococcus), can lead to either urethritis or epididymitis [288]. Urethritis is accompanied by such symptoms as purulent discharge from the penis, dysuria, or erythema at the meatus [288]. Epididymitis caused by gonococcal infection is usually associated with unilateral testicular pain and no other symptoms [288]. Disseminated infection is rare (1% to 3%) [289]. A diagnosis of gonorrhea is confirmed by Gram stain and culture of urethral discharge or swab specimen for *N. gonorrhoeae*, or by nucleic acid amplification testing done on a urine sample [173; 288]. Both techniques have similar sensitivity and specificity [173].

The CDC recommends that all individuals who are evaluated for gonorrhea should also be evaluated for chlamydia, syphilis, and HIV infection [173]. In one study of more than 3,800 men and women, approximately 10% to 30% of individuals with gonorrhea had concomitant infection with chlamydia [290]. The typical lesions of genital HSV-2 in men appear on or around the penis and are first noted as either a single or multiple erythematosus macular lesion(s). However, these lesions are absent in many infected individuals [173]. Viral culture is the preferred test for the diagnosis of HSV-2, but it requires two to seven days for results. The sensitivity of viral culture depends on the quality of the sample and the

time at which the sample is obtained; sensitivity declines as the lesion begins to heal. A PCR test is available and is suggested by the CDC for analysis of cerebrospinal fluid when central nervous system disease is suspected [173]. Type-specific serologic tests are available as laboratory assays and point-of-care tests [173]. These tests have varying degrees of sensitivity for the detection of the HSV-2 antibody (80% to 90%) and specificity of at least 96% [173].

Treatment Options

What is the recommended first-line treatment for gonorrhea?

The treatment of STIs has four main goals [173]:

- Eradicate infection
- Alleviate symptoms and signs
- Decrease complications (infertility, chronic pain, dissemination of disease)
- Prevent transmission

The CDC has developed comprehensive guidelines for the treatment of STIs, last updated in 2021 (***Table 16*** and ***Table 17***) [173]. For chlamydia, gonorrhea, or syphilis, single-dose regimens generally offer an advantage for the treatment of individuals with poor healthcare-seeking or compliance behaviors [173]. The CDC notes that for the treatment of syphilis, neither combinations of benzathine penicillin and procaine penicillin nor oral penicillin preparations are considered appropriate and emphasizes the importance of distinguishing the standard benzathine penicillin product widely used in the United States (Bicillin L-A) from the combination benzathine-procaine penicillin (Bicillin C-R); the latter is not appropriate for the treatment of syphilis [173].

In addition to antibiotic treatment, bed rest, scrotal elevation, and analgesics can help to alleviate symptoms such as fever and local inflammation, which are primarily associated with gonorrhea. Beginning treatment as early as possible decreases the likelihood of complications and spread of infection, especially in the case of syphilis [173]. To prevent the transmission of infection, a patient with a confirmed or suspected STI should be told to avoid sexual contact until therapy is completed and he (and/or his partner) no longer has symptoms [173]. The need for sexual partners to be evaluated for treatment should also be emphasized. State and local health departments may provide assistance in arranging for the evaluation and treatment of sex partners of infected men.

HSV-2

The antiviral medications used to treat HSV-2 can only partially control the signs and symptoms of infection; they cannot eradicate the virus or reduce the risk, frequency, or severity of recurrence after the treatment course has been completed [173]. Men with HSV-2 infection should be given medication for episodic treatment of recurrent infection; treatment should begin within one day after the onset of a lesion [173]. If recurrences are frequent (six or more within a year), long-term suppression therapy may be appropriate; such therapy has been shown to reduce the frequency of recurrence by 70% to 80% [173].

Follow-Up

Peterman et al. found a 14.7% rate of reinfection among men during the first year after treatment for an STI [291]. An unexpected finding in the study was the high percentage (66%) of asymptomatic infections. The authors suggested that treated individuals be rescreened at three months. The CDC recommends follow-up with clinical examination and serologic evaluation at 6 and 12 months after treatment [173].

All states require that cases of chlamydia, gonorrhea, syphilis, HIV, and acquired immune deficiency syndrome (AIDS) be reported to local health authorities [173]. Clinicians should seek advice from state or local health departments if reporting requirements are unclear [173].

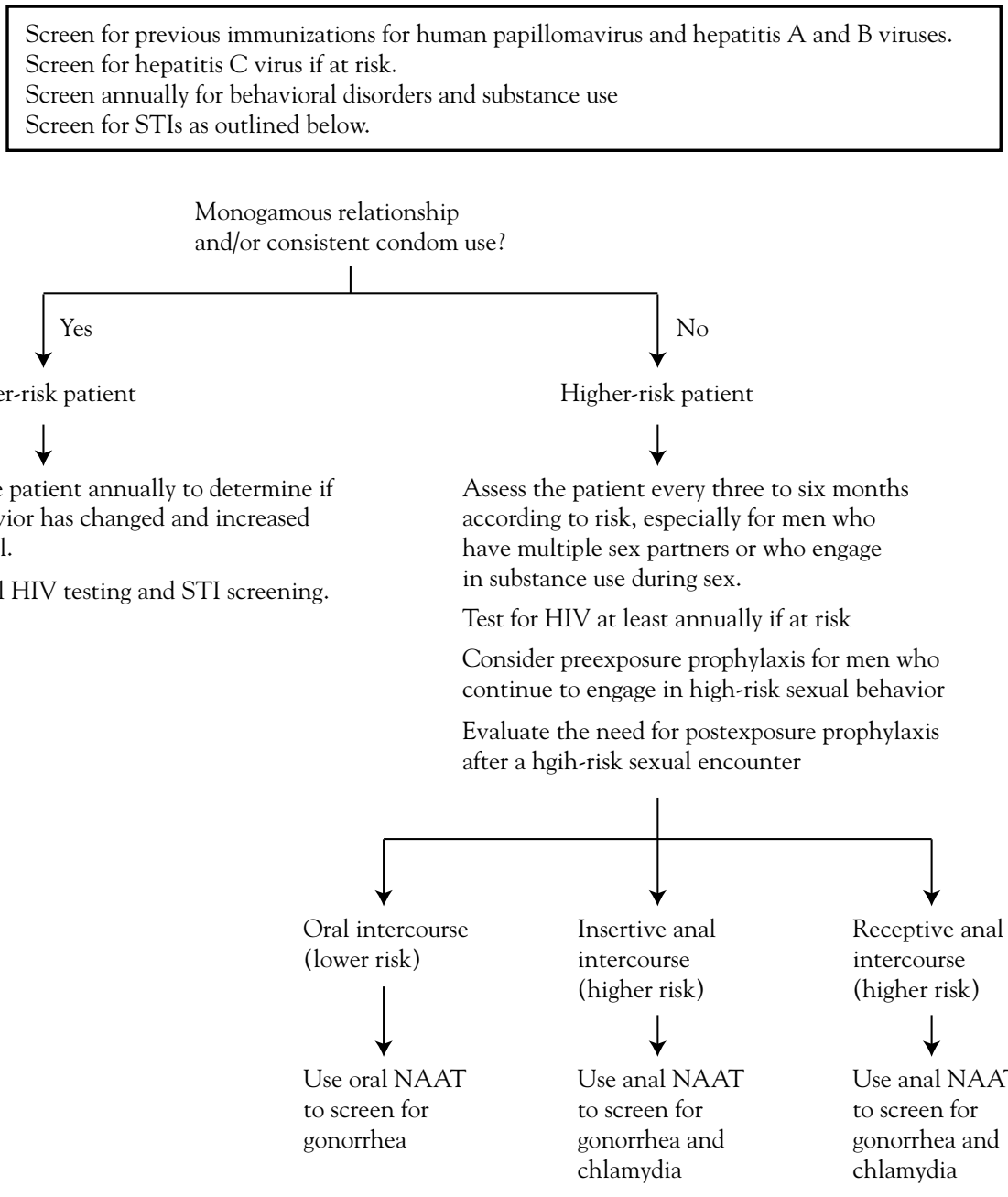
HEALTH ISSUES FOR MEN WHO HAVE SEX WITH MEN

How frequently should men who have sex with men be screened for STI risk?

It is difficult to determine an accurate percentage of MSM in the overall population because of the under-reporting of sexual behavior, but surveys indicate that this group of men represents at least 4% and up to approximately 16% of the population seen by any given healthcare professional [58; 292; 293]. The population that includes MSM (made up of gay, bisexual, and transgender individuals) has been identified as one of the six most underserved groups in the United States, yet medical training and standard resources for healthcare providers lack information on addressing the routine health concerns of this population [292; 294]. MSM have specific healthcare needs that clinicians must understand in order to provide appropriate, comprehensive care.

Perhaps the most important health risk for MSM is their avoidance of routine health care [293]. MSM do not seek routine health care for a variety of reasons. They may have difficulty coming to terms with their sexual identity, fear being judged by healthcare professionals, or be embarrassed to discuss their sexual behavior. In addition, many MSM do not recognize their health risks or their need for screening and preventive health care [58; 294]. Health risks also may not be recognized by MSM who do seek health care, and they may not be forthcoming about sexual behavior [294; 295]. A study has indicated that less than 20% of MSM had discussed their risk of HIV infection with their healthcare provider [296].

ALGORITHM FOR SCREENING MEN WHO HAVE SEX WITH MEN



NAAT = nucleic acid amplification testing.

Source: Reprinted with permission from Preventive health care for men who have sex with men. June 15, 2015, Vol. 91, No. 12, American Family Physician. Copyright © 2015 American Academy of Family Physicians. All rights reserved. *Figure 3*

Creating a welcoming clinical environment is the first step in fostering an open dialogue between healthcare providers and MSM [240; 295]. Among the factors that contribute to such an environment are educational materials about specific healthcare needs for gay and lesbian individuals, a posted statement of nondiscriminatory care, and forms that contain more inclusive choices and gender-neutral language [240; 295]. In addition, healthcare professionals and office personnel should maintain a nonhomophobic attitude, communicate clearly and sensitively using gender-neutral terms, and recognize how their own attitudes affect clinical judgments [293; 297]. Confidentiality is an important issue for MSM, and healthcare personnel should assure the patient that some information could be kept out of the medical record [240].

Comprehensive health care for MSM must focus on the population's disproportionate risks for several conditions, including STIs, anal and other types of cancer, substance misuse, eating disorders, suicide, and victimization [294]. Thus, it is essential for clinicians to address several issues with MSM [58; 173; 292; 298]:

- Use of safe sexual practices
- Screening and immunization for hepatitis A and B viruses
- Testing and consideration of pre-exposure prophylaxis for HIV infection
- Routine screening for STIs
- Routine screening for anal HPV-related neoplasia
- Potential risk for specific cancers (testicular, Hodgkin lymphoma, Kaposi sarcoma)
- Assessment of substance misuse (tobacco, alcohol, cocaine, methamphetamine)
- Nutrition and exercise
- Evaluation of psychologic well-being and mental health
- Screening for violence

Health risks should be addressed at the patient's first visit and each subsequent visit [58]. An algorithm has been developed to help guide recommended screening for MSM (***Figure 3***) [58]. In addition, because of an increased risk of HPV-related cancer, the ACIP now recommends HPV vaccination for MSM up to 26 years of age if they did not receive the vaccine when they were younger [276].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The CDC recommends clinicians should evaluate all adult and adolescent patients who are sexually active or who are injecting illicit drugs and offer to prescribe pre-exposure prophylaxis to persons whose sexual or injection behaviors and epidemiologic context place them at substantial risk of acquiring HIV infection.

(https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf. Last accessed June 6, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Sensitivity should be used in obtaining the medical and sexual history, and the sexual history should be placed in context by emphasizing that an understanding of sexual behaviors is essential to evaluating risks and providing optimal care. It should also be noted that a sexual history is an important component in the care of all patients, regardless of their sexual orientation or behaviors. Because of the various stages a man may be in with respect to his sexual identity, care should be taken to distinguish sexual behavior from sexual identity [295; 297].

It is also vital to have resources readily available to provide to MSM as needed. Such resources include information on STI clinics, substance misuse facilities, services for victims of abuse, and referrals for counseling. The Gay and Lesbian Medical Association (GLMA) has developed resources to help clinicians provide appropriate care to gay, lesbian, bisexual, and transgender individuals. The GLMA also has a guideline for the care of this population, and the brochure (available at http://www.glma.org) includes a variety of additional resources [295].

HEALTH ISSUES FOR TRANSMEN

It is likely that most healthcare providers will encounter transgender individuals in the course of their professional careers, and all healthcare agencies and providers should be prepared to provide competent and compassionate care for gender-variant individuals. Based on data from 2008, the prevalence of female-to-male (FTM) transsexualism (transmen) is 1 in 30,400–200,000 [362]. A transman is a transgender individual who, assigned female at birth, currently identifies as a man. It is important to note that these patients are men and do not require additional description unless medically necessary.

Caring for transgender individuals is complex and requires some preparation and forethought, taking into account knowledge of anatomical reassignments, the effects of therapy, and cultural sensitivity. Very little has been published regarding the unique ongoing healthcare needs of patients who have undergone gender confirmation. In general, health care should be based on the treatments the patient has received and at what stage he may be in the gender transition. Health promotion awareness and health screening will vary somewhat, but generally the patient will have the same needs as most adult patients in a primary care setting; the patient's gender confirmation process will have little effect on many aspects of health care [363]. Basic preventive services, like sexually transmitted infection testing and cancer screening, can be provided without specific expertise in transgender care [364]. Keep in mind that in some cases, older transmen may not disclose their transgender history to their healthcare providers, as they initially sought treatment at a time when it was common for providers to use very strict guidelines to determine who could and could not receive treatment [365].

For the FTM patient, any residual female organs will require lifelong modified physical exams and risk screenings. These patients may require occasional modified pelvic exams and/or mammograms, and both the provider and the patient may have difficulty finding a comfortable clinical environment

[366]. For FTM individuals, gynecologic examinations can heighten their emotional conflict between self-perception and physical anatomy. Respectful communication that maintains dignity, agency, and control is central to mitigating distress during pelvic exams [367]. The routine physical exam should include a breast exam, Pap test, and assessment of bone health and other possible effects of long-term testosterone supplementation.

PSYCHOSOCIAL WELL-BEING OF MEN

Psychosocial well-being is important to men, and many conditions or situations can disrupt the sense of well-being. Among the more common factors that can have a negative effect on well-being for both sexes are everyday stressors (positive as well as negative), personal conflicts, traumatic events, and depression. In general, men lack the social support and interpersonal relationships that help women to cope with stresses [299]. Because of this, men differ in their ability to handle stress, with many men resorting to anger, violence, and substance misuse to deal with stress or depression [28; 300]. As a result, stress/anger, substance misuse, and depression are among the psychosocial conditions with the most serious health implications for men. Most men will not seek help for psychosocial disorders and may not recognize the symptoms of depression [45; 300; 301]. Thus, it is important for healthcare providers to address psychosocial well-being and potential threats to well-being as part of routine health evaluations of men.

STRESS/ANGER

Stress and anger have long been associated with negative health consequences. Most of the earlier research focused on the effects of stress and hostility on coronary heart disease, and additional research has found a link between hostility and a more rapid decline in lung function in older men [302; 303; 304]. Appropriate expression of anger has been suggested as a way to improve health, and controlling anger has been shown to promote well-being in older individuals [305].

Safety is also of concern, as anger has been associated with an increased incidence of injuries and violence. In one study, higher levels of anger (at a given moment) were associated with an increased risk of injury, especially in men [306]. In that study, nearly 32% of individuals who had been injured reported having some degree of irritability before the injury. Men are the usual perpetrators of intimate partner violence causing injury, and these men tend to be younger (18 to 35 years of age), to be from a racial/ethnic minority population, and to have low socioeconomic status [307; 308]. Substance misuse and unemployment are also associated with such violence [307]. However, identifying a perpetrator of intimate partner violence in a clinical setting is difficult [308]. It is important to remember that men can also be victims of intimate partner violence, and this is especially true for MSM [309].

Although the USPSTF found insufficient evidence for or against routine screening for intimate partner violence (including child abuse and elder abuse), a survey of patients within a private family practice network showed that 97% of respondents believed that physicians should ask patients about family stress and conflict [310; 311]. The survey sample included women who had been physically hurt by intimate partner violence as well as men who had admitted perpetrating such injury. These findings support early studies that indicated patient preference for clinicians to ask questions about physical and sexual abuse [312]. The American Academy of Family Physicians (AAFP) notes that family physicians have the opportunity to provide early intervention in family violence through routine screening and identification of abuse; thus, physicians should be alert for the presence of family violence in virtually every patient encounter [313]. It seems reasonable and appropriate for clinicians to include within routine health assessments of men questions about feelings of anger and frustration and urges to strike family members [307; 309]. Suggestions for strategies that focus on anger management and conflict resolution may be helpful, especially for adolescents and young men [309].

SUBSTANCE MISUSE

As noted, substance misuse is higher among men than among women in all age categories, and men are more likely to have psychosocial problems related to the misuse [28; 307]. Although the rate of alcohol misuse is highest among younger men, men older than 65 years of age are of special concern because they are much more likely than women to be "problem" drinkers and to misuse a wide range of illicit as well as prescription drugs [307]. As the general population ages, the misuse of illicit drugs is expected to increase [314]. Adding to this problem is the low rate of screening for alcohol misuse in the older population and the secrecy of many men about drug use [314; 315].

Additional concerns are the use of anabolic steroids among adolescents and young adult men and the use of methamphetamine among MSM. Use of anabolic steroids begins during the teenage years in approximately 25% of cases, and about 10% of all users are teenagers [316]. The prevalence of methamphetamine use among MSM is approximately 10% to 20%, a rate that is 10 times higher than that in the general population [317].

Several professional organizations, including the USPSTF, recommend screening and behavioral counseling intervention to reduce alcohol misuse [318]. However, reported rates of screening have been low [319]. Several screening instruments have been developed, and they vary in the number of questions, the populations for which they are best suited, and their usefulness in specific situations; no one tool is perfect [320; 321; 322; 323]. The CAGE questionnaire, which includes four questions, is best for detecting alcohol dependency and is easy and quick to perform [320; 321]. However, the test may not detect low, but risky, levels of drinking [307; 324]. The Alcohol Use Disorders Identification Test (AUDIT) is the most accurate for detecting problem drinking [319; 322].

Screening in the older population is especially important, as low levels of alcohol use can cause morbidity due to age-related physiologic changes, comorbidities, and the use of prescription medications [325]. Screening tools developed specifically for older individuals should be used, such as the geriatric version of the Michigan Alcohol Screening Test (MAST) or the Alcohol-Related Problems Survey (ARPS) [325; 326; 327]. Clinicians should also ask specific questions about drug use.

A medical history is also helpful, and a family history of alcoholism is a risk factor [319]. Clues to a problem with alcohol can be provided by such symptoms as amnesic episodes, mood swings, chronic fatigue, gastrointestinal symptoms, anxiety, and excessive sweating [319]. Several physical findings can suggest that a patient has a problem with alcohol or drugs, including [319; 324]:

- Mild tremor
- Unsteady gait
- Tachycardia
- Odor of alcohol or marijuana
- Enlarged, tender liver
- Nasal irritation (cocaine use)
- Conjunctival irritation (marijuana use)
- Excessive use of aftershave or mouthwash
- Signs of chronic obstructive pulmonary disease, hepatitis B or C, or HIV infection

Signs that should raise a "red flag" about substance misuse are frequent absences from work or school, history of frequent trauma or accidental injuries, depression or anxiety, other substance misuse, labile hypertension, sexual dysfunction, sleep disorders, poor nutrition, gastrointestinal symptoms, and interpersonal conflicts [307; 319; 324].

Clinicians should provide brief interventions, such as short counseling strategies, for men who are identified to have at-risk drinking. These interventions have been shown to be effective [284; 319; 324]. Alcoholism and drug addiction are best treated by an addiction medicine specialist or through an inpatient or outpatient program [324]. Primary care providers should have referrals for counseling and treatment readily available, as well as resources on support groups, such as Alcoholics Anonymous and Narcotics Anonymous.

To help healthcare professionals carry out the appropriate diagnosis and treatment of patients with alcohol problems, the National Institutes on Alcoholism and Alcohol Abuse (NIAAA) developed the publication *Helping Patients Who Drink Too Much: A Clinician's Guide*, which features an updated guideline on screening and brief intervention. The most recent edition is available on the NIAAA website at https://pubs.niaaa.nih.gov/publications/practitioner/cliniciansguide2005/guide.pdf.

DEPRESSION

Depression is often regarded as a "woman's disease" because it is diagnosed more frequently in women than men. However, researchers and the health community at large now realize that depression is of serious concern in men and is underdiagnosed [28; 328]. According to data from 2020, the prevalence of major depressive episode was 6.2% among men and 10.5% among women [329].

Despite the lower rates of depression in men compared with women, the rate of completed suicide is nearly four times higher for men (25.8 vs. 7.1 per 100,000) [25]. Suicide is a leading cause of death for men in many age groups and across all racial/ethnic populations, except for the Black population [25].

The underdiagnosis of depression in men involves clinician-related and patient-related factors. Clinicians' lack of appropriate training and discomfort with dealing with depression contribute to a low rate of diagnosis, estimated to be about 50% [3; 330]. In addition, no screening instrument for suicide risk has been shown to reliably detect suicide risk in primary care populations [331]. This is unfortunate, as primary care providers appear to be in a position to intervene. As many as 83% of people who died by suicide had contact with their primary care physician in the year before death, with approximately 20% seeing their physician one day before death [330; 332]. In addition, 50% to 66% of individuals who committed suicide saw their primary care physician within one month of their death, with 10% to 40% committing suicide within one week of the visit [331]. Thus, better recognition of depression and suicide risk by primary care providers may help reduce suicide rates.

Many patient-related factors in the underdiagnosis of depression are primarily related to gender issues, including [28; 300; 328; 330; 333; 334]:

- Reluctance of men to seek help
- Lack of men's recognition of the symptoms of depression
- Hesitancy of men to express emotions

- Tendency for men to see depression as a weakness
- Men's misconceptions about mental illness and its treatment

Diagnosis

Because men are less likely to express their emotions, they may recognize and discuss only the physical symptoms of depression, making diagnosis a challenge [300; 301; 333]. A carefully taken history can elicit information about risk factors, which include a family history of depression, the use of some medications (beta blockers, histamine H2-receptor antagonists, benzodiazepines, and methyldopa), chronic illness or other comorbidity, lack of social support, recent life stressor, and single marital status [307; 335]. Substance misuse frequently occurs concomitantly with depression, more often in men than women, but the direction of the causal relationship is not clear [300; 335].

Many of the symptoms of depression reported by women are the same for men: depressed mood, changes in appetite and sleep habits, problems with concentration, and an inability to find pleasure in once pleasurable activities [300]. It has been proposed that the symptoms of depression in men represent a male depressive syndrome, characterized by such symptoms as irritability, acting-out, aggression, low tolerance of stress, low impulse control, tendency to blame others, and a greater willingness to take risk [28; 300; 330; 333]. Men with depression may thus present with a very different symptom profile [328].

Identification of suicide risk is an essential component of the evaluation of patients with depression. Many of the risk factors for suicide are similar to those for depression; when the circumstances surrounding completed suicides were reviewed, the following were found to be factors [25]:

- Loss of a partner (through death or other means)
- Loss of job
- History of mental illness
- Depressed mood
- Previous suicide attempts
- Physical health problems
- Intimate partner problem
- Preceding or impending crisis (within two weeks)
- Financial problem

Clinicians should ask questions to determine the duration of symptoms and explore possible triggers of depression [328]. Because of their lack of experience with discussing emotions, many men may be uncomfortable with open-ended questions such as, "How do you feel?"; rather, discussing emotions in situational contexts can help men better express what they are feeling and why [333]. It may also be helpful to de-emphasize the negative connotation of depression and frame questions within the overall context of health and well-being [314].

Treatment Options

Which depression treatment approach offers the best results for most men?

The treatment approach will depend on the severity of symptoms and the patient's preference. In general, a combination of psychotherapy and pharmacologic management provides the best results for most men [328; 335]. Potential psychotherapy approaches include cognitive behavior therapy and interpersonal psychotherapy [300; 307; 328]. First-line pharmacologic treatment involves the use of selective serotonin reuptake inhibitors, such as paroxetine, sertraline, and fluoxetine [307]. This treatment approach has efficacy rates of 30% to 70% [328]. Clinicians should emphasize the importance of taking the medication as prescribed, as it may be two to four weeks before a benefit is evident [328]. Depression that is associated with chronic illness is often seen as an inevitable consequence of the disease, but the depression should be treated. Frequently, the treatment improves the overall outcome [335].

FOSTERING ENHANCED HEALTH BEHAVIORS IN MEN

The strong association between lifestyle choices and men's morbidity and mortality clearly demonstrates the need to foster healthier behaviors among men. Creating a better understanding of the importance of health care requires broad-scale campaigns to heighten awareness of the need for routine and preventive health care and to encourage men to schedule physician visits. Also needed are efforts at the community and practice levels to enhance health-seeking behavior and improve men's understanding of their health. The efficacy of all of these efforts depends on addressing the unique features of the masculine gender identity.

LARGE-SCALE CAMPAIGNS

Which approach may be effective for educating younger men about health issues?

The Men's Health Network has established International Men's Health Week as the week leading up to Father's Day each June [336]. Highlights of the Week include health fairs, screening, and distribution of educational materials in workplaces and elsewhere in the community. Other Men's Health Network campaigns "speak" to men, with names such as "Men at Work" and "Time Out for Men's Health" maintenance schedule [336].

Some have suggested that large-scale campaigns that feature well-respected athletes and actors can increase appeal to men [45]. However, others have cautioned that, while celebrity endorsement of screening may have a positive effect on men, such campaigns may not target the right audience or address all the pertinent facts [337].

The optimal educational campaigns are those that target men and attempt to challenge men's perceptions of health and the need for preventive care. For example, to heighten awareness about depression in men, the National Institute of Mental Health launched the "Real Men, Real Depression" campaign and produced an accompanying booklet "Men and Depression" [335]. Both the campaign and the booklet feature quotations and vignettes from men who have been treated for depression.

Analysis of data about men who lack a usual source of care indicates that such men are more apt to be younger, Hispanic, single (never married or divorced), without insurance, and living in the southern or western parts of the United States or in urban areas [39]. Education about the importance of health care should be provided through public service announcements, media, schools, and workplaces as appropriate to target these groups of men [39]. Given men's propensity to see a physician only when they are sick or have symptoms, educational messages should emphasize the importance of preventive visits and discourage symptoms as a motivator for seeking health care [338]. Resources should also be culturally appropriate for diseases and conditions that disproportionately affect men of certain races and ethnicities.

As a result of men's reluctance to seek help, educational strategies that provide anonymity may be particularly well-suited for them [45; 339]. Print resources should be distributed through a variety of venues that men frequent, such as the workplace, schools, religious organizations, sports arenas, men's organizations or clubs, pubs, supermarkets, car and motorbike dealerships, and barbershops [45; 339; 340]. In addition, digital media may be effective, especially for younger men. A study showed that 90-second educational video clips on men's health, sent by e-mail, were well-received [341].

Many community-based educational programs targeting men have been successful, especially among men in racial/ethnic minority populations. For example, a culturally tailored, language-concordant navigator program was successful at improving rates of colorectal cancer screening at a healthcare center serving a low-income, ethnically and linguistically diverse community [342]. The Black Barbershop Health Outreach Program (BBHOP) has been an effective program for promoting cardiovascular health, and the program can be used as a model for other health topics [343]. Another barbershop-based program involves training barbers to educate their clients about prostate cancer [344]. Focus groups of men from churches of a variety of denominations have indicated that church-based education may also be effective [35; 345].

PRACTICE-LEVEL STRATEGIES

Men are more likely to use healthcare services that are quick and easy; consequently, making physician visits more convenient may increase the number of men who seek health care [339; 346]. Evening office hours and walk-in appointments may be helpful in addressing this problem, and male-specific group appointments have been effective in enhancing men's education on health issues, with high satisfaction reported by participants [347]. In addition, nontraditional settings for healthcare services have been suggested, such as within workplaces and near sports venues, shopping centers, and men's organizations [45; 339].

Men who are most likely to seek preventive care are those who live with a spouse or partner [348]. In addition, men have been shown to have strong feelings about women as the arbiters of health for the entire family and are likely to be influenced to seek health care by a member of the opposite sex; this is especially true for men in racial/ethnic minority populations [35; 40; 43; 45]. Given these findings, healthcare providers should talk to their female patients to emphasize the importance of encouraging the men in their families to seek routine health care. Additionally, all interactions with male patients should be used to promote routine health assessments. Men who seek help for acute problems should be reminded of the need for screening and be counseled about risk factors [45; 349]. A subsequent visit should be encouraged, and this message may be reinforced by providing a take-home reminder or by scheduling an appointment while the patient is in the office [45].

As noted earlier, fostering open communication in a nonjudgmental manner is essential. Clinicians should take care to raise health issues with their male patients and to overcome some masculine traits in communication, such as a reluctance to ask questions [240]. Asking open-ended questions may be helpful in some cases, and providing a questionnaire before the visit may foster discussion [45]. Assumptions about a man's willingness to share information should be avoided, as men have been more forthcoming when they receive cues that they are expected to provide valuable information [350]. Lastly, men often have a need to feel empowered, and shared decision making is important [351].

Decision aids are available in a variety of formats and literacy levels, and they may be useful in helping men make informed decisions about care [119; 129; 130; 131]. Also, clinicians should review decision aids and educational resources carefully before using them to ensure that the information is comprehensive and accurate [129]. Resources should be available about the risks involved with not wearing a safety belt or motorcycle helmet, driving while intoxicated, speeding, handling firearms, stress/anger management, and safety issues in the home and at work.

ONLINE HEALTH RESOURCES FOR MEN
General
American Heart Association *Information on cardiovascular disease, diabetes, cerebrovascular disease; tools for healthy lifestyle habits (diet, exercise, smoking) ("Getting Healthy" section).* https://www.heart.org
Centers for Disease Control and Prevention Men's Health *Area devoted to men's health issues.* https://www.cdc.gov/nchs/fastats/mens-health.htm
Men's Health Network *Site devoted to men's health issues. Publishes Blueprint for Men's Health: A Guide to a Healthy Lifestyle.* https://www.menshealthnetwork.org
Cancer
American Cancer Society *Cancer prevention and early detection worksheet for men—a tool to help men identify risks and understand preventive measures and early detection strategies for prostate cancer and lung cancer; includes links to information on various types of cancer. Information on prevention, screening, diagnosis, and treatment of all types of cancer.* https://www.cancer.org
National Cancer Institute *Information on prevention, screening, diagnosis, and treatment of all types of cancer.* https://www.cancer.gov
National Comprehensive Cancer Network *Patient guides (based on evidence-based guidelines) on the treatment of a variety of cancers.* https://www.nccn.org/patientresources/patient-resources
Smoking Cessation
Centers for Disease Control and Prevention Smoking and Tobacco Use https://www.cdc.gov/tobacco
National Cancer Institute https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco
Genitourinary Disorders
Urology Care Foundation, The Official Foundation of the American Urological Association *Information on benign prostatic hypertrophy, prostate cancer, erectile dysfunction, and other urologic conditions.* https://www.urologyhealth.org
Depression
National Institute of Mental Health *Articles on depression in men, as well as personal stories of men with depression.* https://www.nimh.nih.gov/health/topics/depression
Alcohol and Drug Use
National Institute on Alcohol Abuse and Alcoholism *Research-based information on drinking its effect on health.* https://www.niaaa.nih.gov/alcohol-health
National Institute on Drug Abuse https://nida.nih.gov
Sexually Transmitted Infections
Centers for Disease Control and Prevention Sexually Transmitted Diseases https://www.cdc.gov/std
Source: Compiled by Author *Table 18*

RECOMMENDATIONS AND SUGGESTIONS FOR HEALTH ASSESSMENTS, SCREENING, AND COUNSELING FOR MEN			
Intervention	**Suggested Frequency**	**Relevant Ages (Years)**	**Recommending Body/Source**
Routine physical examination (with determination of height, weight, and body mass index)	Every 3 to 5 years	18 to 39	—
	Every 1 to 2 years	40 to 49	
	Yearly	50 and older	
Blood pressure screening	Every 1 to 2 years, depending on blood pressure	Beginning at 18	USPSTF
Cholesterol level/lipid profile	At least every 5 years	40 to 75 (earlier if at increased risk)	USPSTF
Diabetes (type 2) and prediabetes screening	Every 3 years	35 to 70 in men with overweight or obesity	USPSTF
Cancer-related check-up (for cancer of the thyroid, testicles, lymph nodes, oral cavity, and skin)	At each routine examination	Beginning at 20	ACS
Assessment, Counseling, and Behavioral Interventions as Appropriate			
Tobacco use	At each routine examination	All men	USPSTF
Alcohol use	At each routine examination	All men	USPSTF
Drug (illicit) use	At each routine examination	All men	ASAM
Depression	At each routine examination, when staff-assisted depression care supports are in place	All men	USPSTF
Counseling			
Healthy diet	At each routine examination	Men with risk factors for cardiovascular disease and diet-related chronic diseases	USPSTF
Exercise	At each routine examination	All men	AAFP, AMA, AHA, CDC
Sun avoidance and use of sunscreen	At each routine examination	All men	ACS, AAD, NIH Consensus Panel
Skin examination for melanoma	At each routine examination	All men	ACS
Avoidance of sexually transmitted infections	At each routine examination	All sexually active men at increased risk	CDC
Risk of HIV infection	At each routine examination	All men who have sex with men	AAFP
Risk for hepatitis A and B	At each routine examination	All men who have sex with men and others at high risk	AAFP
Sexual health	At each routine examination	All men	AAFP

Table 19 continues on next page.

RECOMMENDATIONS AND SUGGESTIONS FOR HEALTH ASSESSMENTS, SCREENING, AND COUNSELING FOR MEN *(Continued)*			
Intervention	**Suggested Frequency**	**Relevant Ages (Years)**	**Recommending Body/Source**
Screening			
Colorectal cancer	Every 1 to 10 years, depending on risk and test used	45 to 75	USPSTF
Osteoporosis	At each routine examination	By 65	ACP
HIV	Not established (encourage men to be tested)	15 to 65 (younger and older men at increased risk)	USPSTF
Visual acuity (comprehensive eye examination)	Yearly	Beginning at 65	AAO
Abdominal aortic aneurysm (ultrasonography)	Once	65 to 75 (men who have ever smoked)	USPSTF
Immunizations			
Tetanus, diphtheria, pertussis (Td/Tdap)	Once (Tdap), with booster (Td or Tdap) every 10 years	All men	ACIP
Influenza vaccine	Yearly	All men	ACIP
Pneumococcal vaccine	Once	65 and older (19 to 64 if risk) (one or two doses, depending on vaccine)	ACIP
Hepatitis A	Once	All men, if risk factors are present (2 or 3 doses, depending on vaccine)	ACIP
Hepatitis B	Once	19 to 59, and 60 and older if risk factors are present (2, 3, or 4 doses, depending on vaccine or condition)	ACIP
Human papillomavirus (HPV)	Once	19 to 26 (2 or 3 doses depending on age at initial vaccination and condition) 26 to 45, if desired based on shared clinical decision making	ACIP
Zoster (shingles)	Once	50 and older or younger if risk factors present (2 doses)	ACIP
Haemophilus influenzae type b (Hib)	Once	All men, if risk factors present (1 or 3 doses depending on indication)	ACIP
Meningococcal A, C, W, Y	Once	All men, if risk factors present (1 or 2 doses depending on indication)	ACIP
Meningococcal B	Once	All men, if risk factors present (2 or 3 doses depending on vaccine and indication)	ACIP
Source: [58; 284; 298; 352]			*Table 19*

Clinicians can help ensure that their patients receive reliable online information by posting the addresses of authoritative websites in their office, in print resources, and within the community (***Table 18***). Healthcare providers should be familiar with established guidelines for screening among men in various age categories and should emphasize the relative benefits and disadvantages of screening (***Table 19***). The Electronic Preventive Services Selector (ePSS) is an application for mobile devices that provides USPSTF information on screening and counseling, as well as preventive medication services. The AUA offers the Men's Health Checklist, a compact, downloadable reference for coordinating care of men; it is available at https://www.auanet.org/publications/mens-health-checklist.

Routine health assessments should include screening and counseling about lifestyle factors that have an impact on health, such as substance misuse, diet, exercise, safe sex practices, and sun protection. Education about sun protection and self-examination for moles is especially important given the increase in the lifetime risk for melanoma among men [24]. At each routine visit, healthcare providers should assess each male patient's individual lifestyle, psychosocial, and occupational risks. The high rate of unintentional injury as a cause of death for men calls for increased attention to safety issues.

CONCLUSION

In response to high morbidity and mortality rates among men over the past decade, researchers have focused increased attention on men's health issues. Many factors contribute to health-related gender disparities, but male gender identity is thought to have the most significant impact. The characteristics of the traditional male role (self-reliance, independence, and maintenance of a strong image) cause men to seek health care much less often than women, especially for preventive care. As a result, disease in men may remain undiagnosed until more advanced stages. A tendency for risky behavior, another aspect of the traditional male role, also has a significant effect on men's mortality, as evidenced by unintentional injury being the third leading cause of death among all men. Such behaviors as substance misuse and non-use of protective devices (safety belts, helmets) begin in adolescence and continue into adulthood; across all age-groups, the rates of these behaviors are higher for male individuals than for female individuals. These behaviors are strongly associated with both chronic diseases and all-cause mortality in men.

Prostate cancer is a major concern for many men, and the issues of prostate cancer screening and treatment options are complex and confusing for patients as well as healthcare professionals. Informed decision making is also an important aspect of many benign conditions, such as prostatitis, BPH, premature ejaculation, erectile dysfunction, and late-onset hypogonadism. These conditions have a substantial effect on the quality of life for men, yet men are reluctant to initiate conversations on these topics because of embarrassment and a hesitancy to express feelings and symptoms. It is important to create an environment of open dialogue and ask questions to help men discuss these topics.

The psychosocial well-being of men is important for overall health. Alcohol misuse and depression have both been underdiagnosed in men, especially older men, and clinicians should remain diligent in screening for these disorders in their male patients.

Improvement of men's health relies on men gaining a greater understanding of their risk factors and becoming more involved in the health issues that affect them. Healthcare professionals have a critical role in helping to develop strategies to enhance men's utilization of healthcare resources and in encouraging their male patients to engage in screening and preventive care and to adopt healthy behaviors. Health assessments and screening should be carried out according to established guidelines, with consideration given to each individual patient's specific risks.

Customer Information/Evaluation insert located between pages 44–45.

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AIRWAY MANAGEMENT: BASICS FOR HEALTHCARE PROVIDERS

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Purpose: Gaining control of the airway in a compromised patient is absolutely crucial. The purpose of this course is to provide practitioners, whether in the clinic, the intensive care unit, the emergency room, or in the community as a pre-hospital provider, with the clinical knowledge needed to rapidly and effectively assess the patient's airway and intervene efficiently to begin to ventilate the patient in distress.

Faculty: Richard E. Haas, PhD, CRNA (Retired), LTC US Army Nurse Corps (Retired)

Audience: This course is designed for healthcare professionals involved in monitoring and maintaining patients' airways, including nurses and respiratory therapists.

Additional Approval: AACN Synergy CERP Category A

POSTOPERATIVE COMPLICATIONS

#30763 • 15 ANCC / 1 Pharm Hour

Book By Mail – $83 • **ONLINE – $75**

Purpose: The purpose of this course is to provide nurses and all allied health professionals who care for postsurgical patients the knowledge necessary to recognize and manage common postoperative complications, improving patient care and outcomes.

Faculty: Susan Engman Lazear, RN, MN

Audience: This course is designed for all nurses and allied professionals involved in the care of patients who undergo surgical procedures, especially those who work in the preoperative area, the operating room, or the postanesthesia unit in hospitals or free-standing surgical centers.

Additional Approval: AACN Synergy CERP Category A, CCMC

RENAL DISEASE AND FAILURE

UPDATE

#34233 • 10 ANCC / 5 Pharm Hours

Book By Mail – $58 • **ONLINE – $50**

Purpose: The purpose of this course is to provide primary care clinicians with the information necessary to appropriately identify and treat renal disease, with the objective of minimizing the long-term effects and complications of the disease.

Faculty: Carol Whelan, APRN

Audience: This course is designed for nurses involved in the care of patients with kidney disease or failure.

Additional Approval: AACN Synergy CERP Category A, CCMC

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THYROID DYSFUNCTION

UPDATE

#38503 • 4 ANCC / 2 Pharm Hours

Book By Mail – $28 • **ONLINE – $20**

Purpose: As a result of the high prevalence of thyroid conditions, nurses and other healthcare providers encounter thyroid dysfunctional patients every day. The purpose of this course is to provide the most current information regarding thyroid disease diagnosis, treatment, and management to facilitate early diagnosis and treatment and optimum patient outcomes.

Faculty: Marilyn Fuller Delong, MA, BSN, RN

Audience: This course is designed for nurses, allied surgical professionals, and other healthcare workers in all practice settings who may care for patients with thyroid dysfunction.

Additional Approval: AACN Synergy CERP Category A, CCMC

MIGRAINE: DIAGNOSIS AND THERAPEUTIC ADVANCES

#90072 • 5 ANCC / 5 Pharm Hours

Book By Mail – $33 • **ONLINE – $25**

Purpose: The purpose of this course are to provide an integrated update of the recent developments on the pathophysiology of migraine and resulting "mechanism-related" therapies, to evaluate the clinical benefit-risk ratio of antimigraine medications, and to summarize the current and evidence-based guidelines for the clinical management of migraine. The information provided should contribute to a more positive interaction between patients and healthcare professionals, through fostering patient awareness, implementation of lifestyle changes, and compliance to therapy.

Faculty: A. José Lança, MD, PhD

Audience: This course is designed for physicians, physician assistants, nurses, nurse practitioners, and other healthcare professionals involved in the care of patients with known or suspected migraine.

Additional Approval: AACN Synergy CERP Category A, CCMC

ASTHMA: DIAGNOSIS AND MANAGEMENT

#90483 • 10 ANCC / 5 Pharm Hours

Book By Mail – $58 • **ONLINE – $50**

Purpose: Asthma is increasingly common, and most healthcare professionals will encounter patients with the condition. The purpose of this course is to provide nurses and pharmacy professionals with up-to-date, accurate information regarding the diagnosis and management of asthma and long-term outcomes for those with the condition.

Faculty: Sharon M. Griffin, RN, PhD; Patricia Walters-Fischer, RN, BS

Audience: This course is designed for nurses, pharmacists, and pharmacy technicians who may care for patients with asthma.

Additional Approval: AACN Synergy CERP Category A, CCMC

Prices are subject to change.
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Course Availability List *(Cont'd)*

COLORECTAL CANCER
#90782 • 15 ANCC / 5 Pharm Hours
Book By Mail – $83 • **ONLINE – $75**
Purpose: The purpose of this course is to provide healthcare professionals with information regarding the screening, diagnosis, and treatment of colorectal cancer in order to improve adherence to established guidelines and, by extension, patient outcomes.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, physician assistants, nurses, and other healthcare providers who may improve the identification and care of patients with colorectal cancer.
Additional Approval: AACN Synergy CERP Category A, CCMC

DIAGNOSING AND TREATING OVERWEIGHT AND OBESE PATIENTS
#91573 • 5 ANCC / 2 Pharm Hours
Book By Mail – $33 • **ONLINE – $25**
Purpose: Obesity is an epidemic in the United States. As statistics indicate that the problem is growing, the purpose of this course is to educate healthcare professionals about the epidemiology and treatment of overweight and obese patients. Clinical management, presentation, diagnosis, and behavioral and medical management will be reviewed to assist healthcare professionals in encouraging their patients to lose weight and prevent obesity-related comorbidities.
Faculty: John J. Whyte, MD, MPH
Audience: This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients who are overweight or obese.
Additional Approval: AACN Synergy CERP Category A

AUTISM SPECTRUM DISORDER
UPDATE
#92203 • 5 ANCC / 1 Pharm Hour
Book By Mail – $33 • **ONLINE – $25**
Purpose: The purpose of this course is to provide healthcare professionals with a basic understanding of the very complex, misunderstood, often puzzling, and sometimes disabling condition, enabling them to provide more thorough patient care, recognize symptomatology, and educate patients, families, teachers and communities about autism spectrum disorder.
Faculty: Sharon M. Griffin, RN, PhD
Audience: This course is designed for healthcare professionals in all practice settings who may be involved in the care of patients with an autism spectrum disorder.
Additional Approval: AACN Synergy CERP Category A, CCMC

RESPONSIBLE AND EFFECTIVE OPIOID PRESCRIBING
Opioid/ Controlled Substances
#95151 • 3 ANCC / 3 Pharm Hours
Book By Mail – $23 • **ONLINE – $15**
Purpose: The purpose of this course is to provide clinicians who prescribe or distribute opioids with an appreciation for the complexities of opioid prescribing and the dual risks of litigation due to inadequate pain control and drug diversion or misuse in order to provide the best possible patient care and to prevent a growing social problem.
Faculty: Mark Rose, BS, MA
Audience: This course is designed for all physicians, osteopaths, physician assistants, pharmacy professionals, and nurses who may alter prescribing practices or intervene to prevent drug diversion and inappropriate opioid use.
Additional Approval: AACN Synergy CERP Category A, CCMC
Special Approvals: This course is designed to meet the requirements for opioid/substance abuse education.

MEDICAL MARIJUANA AND OTHER CANNABINOIDS
#95172 • 5 ANCC / 5 Pharm Hours
Book By Mail – $33 • **ONLINE – $25**
Purpose: The purpose of this course is to provide healthcare professionals with unbiased and evidence-based information regarding the use of marijuana and other cannabinoids for the treatment of medical conditions.
Faculty: Mark Rose, BS, MA, LP
Audience: This course is designed for physicians, nurses, physician assistants, pharmacists, social workers, therapists, and counselors in the primary care setting involved in the care of patients who use or who are candidates for the therapeutic use of marijuana or other cannabinoids.
Additional Approval: AACN Synergy CERP Category A, CCMC

PSYCHOPHARMACOLOGY
NEW!
#95230 • 10 ANCC / 10 Pharm Hours
Book By Mail – $58 • **ONLINE – $50**
Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the information necessary to appropriately prescribe, administer, and dispense psychopharmacotherapy, with the ultimate goal of improving patient care and public health.
Faculty: Carol Whelan, APRN
Audience: This course is designed for nurses and pharmacy professionals involved in the care of patients with mental health conditions.
Additional Approval: AACN Synergy CERP Category A

ALZHEIMER DISEASE
UPDATE
#96153 • 15 ANCC Hours
Book By Mail – $83 • **ONLINE – $75**
Purpose: In order to increase and maintain a reasonable quality of life for patients with Alzheimer disease throughout the course of the disease, caregivers must have a thorough knowledge and understanding of the disease. The purpose of this course is to provide clinicians with the skills to care for patients with Alzheimer disease in any setting as part of the interdisciplinary team.
Faculty: Joan Needham, MSEd, RNC
Audience: This course is designed for clinicians who come in contact with patients with Alzheimer disease in hospitals, long-term care facilities, home health care, and the office.
Additional Approval: AACN Synergy CERP Category A, CCMC

ATTENTION DEFICIT HYPERACTIVITY DISORDER
UPDATE
#96213 • 5 ANCC / 2 Pharm Hours
Book By Mail – $33 • **ONLINE – $25**
Purpose: Attention deficit hyperactivity disorder (ADHD) has a significant effect on day-to-day functioning and quality of life; however, it often goes unrecognized. The purpose of this course is to educate healthcare professionals about the epidemiology, diagnosis, and management of ADHD.
Faculty: John J. Whyte, MD, MPH; Paul Ballas, DO
Audience: This course is designed for all physicians, nurses, and social work/counseling groups involved in the care of patients with attention deficit hyperactivity disorder.
Additional Approval: AACN Synergy CERP Category A, CCMC

Prices are subject to change.
Visit www.NetCE.com for a list of current prices.

Course Availability List *(Cont'd)*

DEPRESSION AND SUICIDE

#96403 • 15 ANCC / 2 Pharm Hours

Book By Mail – $83 • **ONLINE – $75**

Purpose: Although contact with the primary care setting represents a potential opportunity for timely identification and intervention, abundant evidence indicates that many patients with depression are inadequately diagnosed and treated in these settings. The purpose of this course is to provide the information and encouragement necessary to allow primary care providers to properly diagnose, treat, and follow-up with patients with depression.

Faculty: Mark Rose, BS, MA, LP

Audience: This course is designed for physicians, nurses, physician assistants, social workers, therapists, and counselors in the primary care setting who may identify and treat patients who are depressed and/or suicidal.

Additional Approval: AACN Synergy CERP Category A, CCMC

ANXIETY DISORDERS IN OLDER ADULTS

#96690 • 3 ANCC / 1 Pharm Hour

Book By Mail – $23 • **ONLINE – $15**

NEW!

Purpose: Older adults are the fastest growing demographic in the world, and anxiety disorders are the most common mental disorder in this age group. The purpose of this course is to provide clinicians with the knowledge and skills necessary in order to improve the assessment and treatment of anxiety disorders in older adults.

Faculty: Beyon Miloyan, PhD

Audience: This course is designed for the benefit of a broad range of allied health professionals, including but not limited to physicians, nurses, medical assistants, and nursing home administrators.

Additional Approval: AACN Synergy CERP Category A

PSYCHEDELIC MEDICINE AND INTERVENTIONAL PSYCHIATRY

#96790 • 10 ANCC / 8 Pharm Hours

Book By Mail – $58 • **ONLINE – $50**

NEW!

Purpose: The purpose of this course is to provide medical and mental health professionals with the knowledge and skills necessary to effectively treat mental disorders using emerging psychedelic and interventional techniques.

Faculty: Mark S. Gold, MD, DFASAM, DLFAPA

Audience: The course is designed for all members of the interprofessional team, including physicians, physician assistants, nurses, and mental health professionals, involved in caring for patients with mental disorders resistant to traditional treatment approaches.

Additional Approval: AACN Synergy CERP Category A

CULTURAL COMPETENCE: AN OVERVIEW

#97430 • 2 ANCC Hours

Book By Mail – $23 • **ONLINE – $15**

NEW!

Purpose: The purpose of this course is to provide members of the interprofessional healthcare team with the knowledge, skills, and strategies necessary to provide culturally competent and responsive care to all patients.

Faculty: Alice Yick Flanagan, PhD, MSW

Audience: This course is designed for all members of the interprofessional healthcare team.

Additional Approval: AACN Synergy CERP Category B

HERBAL MEDICATIONS: AN EVIDENCE-BASED REVIEW

#98394 • 10 ANCC / 10 Pharm Hours

Book By Mail – $58 • **ONLINE – $50**

UPDATE

Purpose: Considering the pharmacological interactions between herbal medications (HMs) and conventional medications, it is paramount to increase the awareness and knowledge of healthcare professionals about HMs. The purpose of this course is to increase healthcare professionals' awareness of the potential risks and benefits of HMs from an evidence-based perspective and promote the planned inclusion of HM use in patients' medical history. This course should allow healthcare professionals to discuss HMs in a knowledgeable and succinct manner with patients and colleagues.

Faculty: A. José Lança, MD, PhD

Audience: This course is primarily designed for physicians, pharmacists, and nurses. However, considering the widespread availability and increased use of herbal medications, other healthcare professionals, including social workers and clinical therapists, will also benefit from this course.

Additional Approval: AACN Synergy CERP Category A, CCMC

SLEEP DISORDERS

#98883 • 10 ANCC / 5 Pharm Hours

Book By Mail – $58 • **ONLINE – $50**

Purpose: Many of the complications associated with sleep disorders are preventable, making early diagnosis and appropriate treatment vital. The purpose of this course is to provide healthcare professionals with the information necessary to identify and effectively treat sleep disorders, thereby improving patients' quality of life and preventing possible complications.

Faculty: Teisha Phillips, RN, BSN

Audience: This course is designed for all healthcare professionals, including physicians, nurses, pharmacists, and mental health practitioners, who are involved in the care of patients experiencing a sleep-related disorder.

Additional Approval: AACN Synergy CERP Category A, CCMC

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☐	90072	Migraine: Diagnosis and Therapeutic Advances / 5	$33
☐	90483	Asthma: Diagnosis and Management / 10	$58
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3. Would you recommend this course to your peers?
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7. Before completing the course, did you identify the necessity for education on the topic to improve your nursing practice?
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9. Has what you think or feel about this topic changed?
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11. Did evidence-based practice recommendations assist in determining the validity or relevance of the information?
12. Are you more confident in your ability to provide nursing care after completing this course?
13. Do you plan to make changes in your nursing practice as a result of this course content?

#90240
Pancreatic Cancer
10 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#93764
Men's Health Issues
15 Contact Hours

1. ☐ New ☐ Review
2. _____ Hours
3. ☐ Yes ☐ No
4. ☐ Yes ☐ No
5. ☐ Yes ☐ No
6. ☐ Yes ☐ No
7. ☐ Yes ☐ No
8. ☐ Yes ☐ No
9. ☐ Yes ☐ No
10. ☐ Yes ☐ No
11. ☐ Yes ☐ No
12. ☐ Yes ☐ No
13. ☐ Yes ☐ No

#90240 Pancreatic Cancer — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

_____

#93764 Men's Health Issues — If you answered yes to question #13, how specifically will this activity enhance your role as a member of the interprofessional team? _____

_____

_____

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