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Learning objectives	• Examine thyroid nodules and the varying degrees of importance and active surveillance in low-risk papillary thyroid carcinoma. • Apply pharmacological evidence to evaluate the use of aspirin compared with enoxaparin following hip and knee arthroplasty, treatment of actinic keratosis, and 5 alpha-reductase inhibitors and prostate cancer. • Discuss medical management concerning Medicare Shared Savings Program (MSSP) and Medicare Advantage (MA), functional cardiac testing after PCI, physical activity and depression and long-term oxygen therapy with moderate hypoxemia from COPD.

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Thyroid nodules: Focus on high value care

Thyroid cancer is one of the most over diagnosed and over treated cancers. In the last 25 years, the diagnosis of thyroid cancer has tripled and most of these cases reflect the detection of small papillary thyroid cancers.[1] The rate of thyroid lobectomy or total thyroidectomy during this same time increased almost six-fold, yet the mortality of thyroid cancer did not change, suggesting that most of these cases represent over diagnosis.

It has been estimated that at least one third of adults harbor small indolent papillary thyroid cancers, the vast majority of which will not produce symptoms during a person's lifetime.[2] A recent survey of 439 endocrinologists and surgeons who regularly treat thyroid cancer compared their recommendations to those of the American Thyroid Association's (ATA). Their recommendations represented overdiagnosis 64% of the time and over treatment 40% of the time when compared to the ATA guidelines.[3] The key issue for PCP's is differentiating between the infrequent, significant thyroid cancers and the frequent ones that are indolent, and not likely to cause clinical disease in the patient's lifetime. When diagnosed, these latter cancers should be managed with active surveillance, as per the ATA recommendations. The goal of assessing a thyroid nodule is therefore to identify those that represent cancers that could cause harm to the patient, and avoid diagnostic workups and treatment of those that would not cause harm.

Fifty percent of adults have thyroid nodules of which only 15% are clinically relevant.[4] Using patient characteristics and known risk factors along with imaging, particularly ultrasound, can help determine which nodules need follow-up. Nodules 1.5 to 2 cm in size can be followed with ultrasound without the need for FNA when there are minimal or no suspicious features. [5,6] Small (under 1-2 cm in diameter) papillary cancers can be safely followed. [7] This conservative approach avoids unnecessary and potentially harmful surgery.[1]

Patient risk factors for thyroid cancer are well appreciated. A thyroid nodule in a male has a 20-30% risk of malignancy; for a female the risk is 10-20%. For patients 50 years of age or younger, 20-30% of nodules are malignant; for those over 50 the figure drops to 10-20%. Thyroid nodularity increases with age, but does not increase the likelihood of cancer in an individual patient.[8] Following assessment of the patient, additional factors known to increase the risk of malignancy include: [5]

- Younger age
- A solid nodule
- Persistent new cervical lymphadenopathy
- Permanent voice hoarseness with evidence of laryngeal nerve compromise
- A family history of medullary thyroid cancer
- Rapid growth of the nodule
- Childhood exposure to ionizing radiation

Ultrasound should not be used to screen for thyroid nodules or thyroid cancer. However, ultrasound is very useful in characterizing significant thyroid nodules discovered on physical exam or incidentally on an imaging study and is the initial imaging test of choice to characterize a thyroid nodule. The incidence of thyroid cancer confirmed with ultrasound guided FNA is between 7 and 15%.[9] The ultrasonic characteristics that help determine the risk of malignancy in a thyroid nodule can be found in Table 1.

Ultrasound characteristics should be coupled with the other risk factors described above to fully characterize an individual's risk of malignancy. Very low-risk nodules (i.e., nodules with a cancer risk of <5%) should be managed only with periodic monitoring. Decision aids are available to assist in discussions with patients about the advantages of monitoring nodules with low-risk cancers.[10] Nodules with intermediate risk (i.e., those with variable risk of malignancy, but without high-risk features or signs of metastasis) in older patients or in patients with substantial comorbid illness may be managed with periodic imaging without the need for FNA. [5,11]

Table 1. [12,13]

Sonographic feature		TIRADS scoring	ATA Scoring (malignant risk)	Malignancy risk (%)
Not worrisome feature	Cystic nodule (CN)	1–2 points	Benign	<2%
	Iso-hyperechogenicity or Hyperechogenicity (HE)			Low risk
Single high-risk feature	Irregular Borders (IB)	3–4 points	Very low to intermediate risk	Low to intermediate risk
	Microcalcifications (MC)			
	Hypoechogenicity (Hypo)			
Multiple high-risk features	Hypo and MC	5 or more points	High risk	Intermediate to high risk
	Hypo and IB			

TIRADS=Thyroid Imaging Reporting and Data Systems ATA=American Thyroid Association

TIRADS grading seems to have a higher diagnostic accuracy [11]

The strategy for management of a thyroid nodule can be guided by a combination of size and sonographic characteristics. Almost all nodules smaller than 1 cm can be followed conservatively without the need for FNA regardless of finding on sonogram.[14] Nodules between 1.5 to 2.0 cm in size and low-risk features on ultrasound (Table 1) can be monitored and those with higher-risk features should be evaluated with FNA. Consideration of comorbid conditions is important in patients over 70 years of age in deciding if a FNA is warranted.

For nodules requiring further evaluation, FNA is the initial gold standard.[5] FNA accurately diagnoses 70% of lesions as benign. [14] Cytologic analysis of the FNA sample is critical. Pathologic categories are outlined in the Table 2, indicating risk of malignancy for each category. A growth rate of more than 2-4 mm (in the nodules largest dimension) per year should be suspicious for malignancy.[15]

Table 2. FNA cytology classification and malignant potential [12]

Cytologic classification	Occurrence in FNA (% of aspirated)	Malignancy overall estimated risk (%)
Non diagnostic or unsatisfactory	2–24	1–10
Benign	55–74	<4
Atypia of undetermined significance	1–18	15–30
Follicular neoplasm	2–25	20–35
Suspicious for malignancy	1–6	60–75
Malignancy	2–8	>97

Use of molecular analysis should be reserved for clinically relevant thyroid nodules when surgery is recommended based on indeterminant FNA cytology.[5] Molecular analysis has no role in routine screening.

Summary: Thyroid cancer is one of the most over diagnosed and over treated cancers. Screening for thyroid nodules is not recommended; thyroid nodules are frequent, increase with age and most are benign. The next most common category are those that represent indolent papillary carcinomas, which are present in up to one third of the population. These are predominantly the ones that fall into the over diagnosis category, in which case treatment can potentially result in patient harm. Small thyroid nodules should not be ultrasonographically followed or indiscriminately evaluated, rather the use of the Optimal Care thyroid nodule algorithm is recommended. (Click the Clinician/Patient Content link on page 10 for algorithm search.) Very low risk and low risk nodules under 1.5-2 cm can safely be followed without FNA as per the ATA guidelines. Ultrasound along with individual patient risk factors can help define which nodules need pathologic examination using FNA. Most patients with small papillary thyroid cancers should be offered active surveillance as the primary course of action.

Active surveillance is a viable treatment option for low-risk papillary thyroid carcinoma

An oft-used example of wasted care is the impact of the South Korean population-based screening program for papillary thyroid carcinoma and resultant impact on diagnosis (vastly increased) and mortality from the carcinoma (unchanged at near zero).[16] For when this most common type of thyroid cancer is diagnosed, active surveillance (AS), rather than surgery, is a viable treatment option. A study recently published in JAMA Oncology[17] and accompanying editorial[18] reinforce this approach. The study furthermore extends the parameters of inclusion for consideration of AS from the current standard of tumor size of 10mm or less and growth of no more than 3mm, to instead be used for patients with low-risk tumors up to 20mm, if growth was less than 5mm and total volume of the nodule did not double (respective yearly incidences were 1.2% and 2.2%). Surgery indications in the study included exceeding these parameters, development of biopsy-confirmed metastatic disease, or patient decision.

In the study, 222 patients with low-risk papillary thyroid CA seen in a California-based health system during the 2014-2021 timeframe were enrolled. 50.5% chose AS whereas the remaining 49.5% chose immediate surgery. Active surveillance consisted of thyroid ultrasound every six months for two years, then annually for the duration of the study if no growth was identified. Mean follow-up was 37.1 months. 90.1% of those in the AS group remained on AS, with 7.1% crossing over to have delayed surgery (half with an indication of 5mm or more of tumor growth, and half due to patient or provider preference). All patients (AS, immediate surgery, and delayed surgery) remain disease free at the latest follow up. There was no significant correlation between initial tumor size and subsequent tumor growth, nor between younger age and subsequent increase in tumor size.

Study authors also examined patient anxiety scores as part of the protocol and determined patients who opted for immediate surgery had higher scores at baseline compared to those who opted for AS, and this difference persisted over time. Anxiety remained high in the immediate surgery group and decreased from baseline in the AS group. After baseline measures, anxiety scores were not assessed in the small subset (8 patients) who underwent delayed surgery.

Although sample size was small and the study was not randomized, findings support consideration of expanded criteria for use of AS in low-risk papillary thyroid CA, and further reinforces the need for shared decision-making to account for patient anxiety levels. Ideally, this SDM conversation should take place at the time of FNA and prior to the diagnosis of thyroid cancer, as this has been shown to markedly increase the use of AS. Of note, more than 70% of diagnosed thyroid cancers in the US are smaller than the 20mm cut-off used in this study of AS.[19]

Aspirin is less effective than enoxaparin in preventing symptomatic venous thromboembolism after hip or knee arthroplasty

Routine use of thromboprophylaxis following total hip and knee arthroplasty improves post-operative morbidity and mortality from thromboembolic events such as pulmonary embolism. Aspirin has been prescribed for thromboprophylaxis, but its efficacy has not been well-studied. Recently, investigators compared aspirin monotherapy with enoxaparin monotherapy following hip and knee arthroplasty and found that aspirin was inferior.[20]

The study used a cluster-randomized, crossover methodology. Hospitals were randomized to administer aspirin (100 mg/d) or enoxaparin (40 mg/d) for 35 days following total hip arthroplasty and for 14 days following total knee arthroplasty. Patients were followed for 90 days to evaluate the primary outcome of symptomatic venous thromboembolism. A noninferiority margin was set at 1%.

Enrollment was stopped after interim analysis. Among 9,203 patients who completed the trial, 256 developed at least one form of symptomatic venous thromboembolism: pulmonary embolism (n=79), above-knee DVT (n=18), and below-knee DVT (n=174). The rate of venous thromboembolism was 3.45% with aspirin prophylaxis versus 1.82% with enoxaparin prophylaxis, which led to early termination of the trial. [20]

Based on this study, monotherapy with aspirin is not as effective as monotherapy with enoxaparin in preventing venous thromboembolic events following hip or knee replacement. This is relevant to primary care as we should recommend enoxaparin prophylaxis to appropriate patients as part of our preoperative evaluations for patients planned for hip or knee arthroplasty.

Treatment of actinic keratosis

A recent study in JAMA Dermatology [21] looked at the incidence of treatment for actinic keratoses (AK's) in patients over age 65 from Medicare claims data. Of five million patients examined, 29% had one or more treatments for AK's over a five year period. 79% of these treatments were by dermatologists, and 79% of patients were treated with liquid nitrogen. If left untreated, AK's can develop into squamous cell carcinoma. Importantly, fluorouracil, which has recently been shown to decrease the incidence of squamous cell carcinoma,[22] was used less than 3% of the time. Randomized trials on the effectiveness of "field therapy" treatment of AK's are limited. A NEJM study [23] compared four different approaches to field therapy in 624 patients, including the three most commonly used in the US: fluorouracil, imiquimod, and photodynamic therapy. Of these three, fluorouracil was effective in 75% of patients compared to 54% with imiquimod and 38% with photodynamic therapy. Patient satisfaction and increase in health-related quality of life were also highest with fluorouracil. Fluorouracil is available as an inexpensive generic. This information is important as treatment of uncomplicated AK's using liquid nitrogen for isolated lesions and topical fluorouracil for field therapy is easily accomplished in the primary care setting.

5 alpha-reductase inhibitors and prostate cancer mortality

5 alpha-reductase inhibitors (5-ARIs), the standard treatment for benign prostatic hyperplasia, are associated with a reduced risk of prostate cancer. Two prospective randomized trials demonstrated that 5-ARIs reduced the incidence of low and intermediate risk prostate cancer. [24,25] There appeared a concern over possible increased rate of high-risk prostate cancer, however this was felt to likely be a detection bias within the trials. 18-year follow up of one of the trials showed no difference in all-cause mortality and a non-significant reduction in prostate cancer specific mortality. Overall, there are a paucity of data looking at the association of 5-ARI use with prostate cancer mortality. To help address this, a population-based study was conducted in Sweden, looking at ~349,000 men who had a PSA test done between 2007 and 2018, and for whom data were analyzed in 2021. [26] Approximately 26,000 of these men were 5-ARI users.

With a median follow-up of 8.2 years, and a median exposure to 5-ARIs of 4.5 years, there were 852 deaths from prostate cancer. There were no differences in all-cause mortality related to 5-ARI use, however 5-ARI use was associated with a lower prostate cancer mortality and this mortality improvement increased with duration of use. For those using a 5-ARI for over 8 years, prostate cancer mortality was 56% lower compared to non-users. Overall, the 5-ARI users had larger prostates, higher PSA's, and a higher rate of PSA testing and biopsy. Therefore, it is still unclear if 5-ARIs inherently suppress or slows the growth of prostate cancer, or if the survival difference is caused by increased monitoring in this population. The authors concluded that 5-ARI treatment does not increase the risk of prostate cancer and may decrease the risk of prostate cancer mortality.

MSSP spending is 23-30% higher than MA spending across four clinical conditions

Several studies have previously documented that Medicare Advantage (MA) provides care that is less expensive than FFS Medicare. However, CMS intended the Medicare Shared Savings Program (MSSP) to be an ACO based care model that could compete with MA in terms of reduced costs. Currently about 47% of Medicare beneficiaries are enrolled in MA and about a third in MSSP. Researchers from the Perelman School of Medicine at U. Penn performed a retrospective economic evaluation using data from 15,763 beneficiaries who were continuously enrolled in MA or MSSP from January 1, 2014, to December 31, 2018, with diabetes, congestive heart failure (CHF), chronic kidney disease (CKD), or hypertension.[27] All participants received care at a single large academic health care system (Ochsner). Propensity matching accounted for variables in demographic characteristics, clinical variables, and socioeconomic variables.

For disease-specific cohorts over the study follow-up period, mean unadjusted per-member per-year (PMPY) spending differences between MSSP and MA were $2,159 (diabetes), $4,074 (CHF), $2,560 (CKD), and $2,335 (hypertension). Adjusted MSSP spending remained 23% to 30% higher than MA spending across the follow-up period in all disease cohorts. Primary care was the only category where spending was higher in the MA population compared to the MSSP population. Outpatient hospital spending contributed the most to higher MSSP overall spending, but inpatient spending was also significantly higher for MSSP in all disease cohorts. Specialist spending was not significantly different between MSSP and MA beneficiaries across all disease cohorts. Quality metrics were similar across both groups.

The drivers of this spending difference are likely multifactorial and complex. These include improved utilization management in MA, differences in benefit design, differences in site of service of outpatient services, and unmeasured socioeconomic factors, to name but a few. This study is one of a growing body of literature demonstrating improvements in the cost of care related to the MA model.

Functional cardiac testing after PCI shows no benefit compared with usual care alone

Evidence is clear that, in stable coronary artery disease in most patients, medical management is as effective as catheter-based therapy for the prevention of major adverse cardiovascular event (MACE), and therefore evaluation with functional testing (e.g., nuclear stress tests) is not indicated.[28,29,30] Indeed, this type of testing may result in unnecessary cardiac catheterization. A recent study titled the POST-PCI trial further shows that functional testing even among high-risk patients after percutaneous coronary intervention (PCI) provides no benefit.[31] This randomized controlled multi-center study examined 1,706 patients who had undergone PCI (96.4% of whom received a drug-eluting stent) and deemed 'high-risk' by anatomical or clinical characterization. This definition of 'high risk' included those with left main disease, bifurcation disease, multivessel disease, diffuse long lesions, chronic renal failure or hemodialysis and diabetes mellitus. Those randomized to functional testing received standard care and underwent a routine nuclear stress test, exercise ECG, or stress echocardiogram roughly one year after randomization. The other group received standard care with no routine functional testing. All patients had routine follow-up every six months for two years after randomization. The primary outcome at two years was a composite of death from any cause, myocardial infarction, or hospitalization for unstable angina. There was no significant difference between the two groups for the primary outcome, nor for the secondary outcomes that were each a component of the primary composite outcome.

Even looking at the secondary outcomes of coronary angiography and repeat revascularization, the differences between groups was small, and directionally suggest that those who undergo routine functional testing at one year are more likely to have repeat testing later, with subsequent higher rates of revascularization, yet without any significant improvement in outcomes. At the two-year follow-up, 12.3% of the functional testing group and 9.3% in the standard care group had angiography, with 8.1% and 5.8% undergoing revascularization, respectively. In summary, this is another study that provides evidence that in stable coronary artery disease, even in high-risk patients with previous PCI, functional testing is not typically indicated and may lead to additional unnecessary and potentially dangerous procedures.

Does physical activity decrease the risk of depression?

Previous studies have shown that increased physical activity is associated with lower rates of depression. A recently published meta-analysis aimed to establish a dose-response between the levels of self-reported activity and incident depression.[32] The meta-analysis included prospective cohort studies that (1) reported at least three levels of activity with corresponding risk estimates of depression, (2) included at least 3,000 adults, and (3) provided at least three years of follow-up. A total of 15 studies met inclusion criteria. The 15 studies comprised 191,130 participants, 2,110,588 person-years.

In this analysis, activity volumes were converted to mMET (marginal metabolic equivalents) hours per week. Investigators used mMET midpoints for activity ranges and multiplied the midpoint values by the hours of activity per week reported by study participants. Light activities (e.g., light housework, light gardening) have a range of 0.5-2 mMETs, so a midpoint value of 1.5 mMET was used. Moderate activity was assigned a midpoint value of 3.5 mMET, and vigorous activity was assigned a value of 7 mMET. The World Health Organization advises 150-300 minutes of moderate activity or 75-150 minutes of vigorous activity per week,[33] which represents ~9-18 mMET-hours per week.

Study participants with half the World Health Organization recommended activity (4.4 mMET-h/wk) had 18% lower risk of depression compared to participants who reported no activity. Adults with 8.8 mMET-h/w had 25% lower risk of depression. Activity levels beyond 8.8 mMET-h/w led to diminishing addition potential benefits and greater uncertainty.

Limitations of the studies include self-reports of activity, which can be biased, and observational methodologies, which cannot establish causality. Confounders could affect both the inclination to be sedentary and the risk of depression.

Although we cannot assume causality, it is reasonable to promote physical activity as one of the potential treatments when patients present with depression. Given that exercise improves general health, has few potential harms, and has minimal, if any, costs, health care providers should promote exercise broadly, regardless of the presence or absence of depression.

Long-term oxygen therapy provides no mortality benefit for patients with moderate hypoxemia from COPD

Long-term oxygen therapy (LTOT) has demonstrated mortality benefit in patients with chronic obstructive pulmonary disease (COPD) and severe persistent hypoxemia . The use of LTOT in other populations has been prescribed based on the assumption of benefit, but limited evidence. A recent systematic review and meta-analysis looked at the mortality benefit of LTOT compared with usual care or ambient air via sham concentrators over a three-year treatment period for patients with COPD who had hypoxemia that wasn't severe and persistent.[34] The investigators included studies that examined patients with COPD and moderate hypoxemia, nocturnal hypoxia with desaturations, or both. They used a cut-off of a PaO2 of 56 mm Hg or higher (roughly SaO2 of 89% or higher) as a marker that the hypoxemia was not 'severe', but rather fell in the 'moderate' range. For nocturnal desaturations, they used the European and American cut-offs of ≥30% nighttime recording with SpO2 of <90% or SpO2 of <90% for ≥5 min with a nadir of ≤85% during the night , respectively. For this study, LTOT was defined as the prescription of low-flow oxygen therapy for 15-18h per day or delivered during sleep time only (nocturnal oxygen therapy).

The authors identified five high-quality trials of LTOT with a combined total of 1,002 patients. They defined a minimally important clinical difference in mortality reduction with LTOT during 3 years of follow up as a 30-40% reduction. The results demonstrated a relative risk of death in the LTOT group of 0.91 (a relative risk reduction of 9%), with the 95% confidence intervals crossing (0.72-1.16). This means that even with reporting results in terms of relative risk, which tends to exaggerate differences compared with reporting using absolute risk reduction, the difference between the LTOT group and the group that did not receive LTOT was not clinically meaningful, if indeed it was present at all. Additional analyses in the paper suggested that quality of life, COPD exacerbation rates or hospitalizations were not different between LTOT and non-LTOT groups, although the data was not as complete as it was for the findings of the lack of mortality risk reduction.

At the population level, prescribing LTOT to patients with COPD and moderate daytime hypoxemia or isolated nocturnal hypoxemia or both, appears to be wasted care in terms of mortality prevention, and may also be wasted care for other measures. As always when interpreting population-level studies, individual factors, complications, comorbidities and disease severity must be considered when making patient-specific decisions.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as Chief Medical Officer from 1995 - 2020. He now serves as the Executive Director of Translational Research for Optum Care and co-leads the Optum Center for Research and Innovation. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the CDC Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine and School of Pharmacy. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt is the evidence-based medicine implementation sage and Senior National Medical Director for Optimal Care. He has been a physician executive for more than 25 years in several academic teaching hospitals, national home care companies and Vizient. He received his Medical Doctorate from the Medical College of Georgia (AOA honors), completed his Internal Medicine and Infectious Disease Fellowship at the University of Minnesota Hospital and Clinics and his MBA at the Carlson School of Management at the University of Minnesota. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine.

He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders. Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons.

Joshua Jacobs, MD, FAAFP

With over 20 years of clinical, academic, and leadership experience regionally, nationally, and internationally. Dr. Jacobs currently serves as primary care engagement lead national Medical Director for Optimal Care within Clinical Performance at Optum Care. He is a Clinical Professor of Family Medicine at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

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