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Learning objectives	• Critically evaluate emerging clinical evidence and assess how new data may inform, refine, or challenge existing standards of care across multiple therapeutic areas. • Apply principles of evidence-based patient-centered decision-making by weighing clinical benefits, risks, costs, and patient preferences when considering diagnostic, surveillance, or treatment strategies. • Identify opportunities to modify or avoid low-value clinical practices, including situations involving overdiagnosis, overtreatment, or unnecessary interventions, in order to improve quality and reduce potential patient harm.

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A different approach to actinic keratosis: The case for active surveillance

Every one of us has had a patient ask about a skin lesion that appeared since their last visit. If that patient is over the age of 50 with evidence of sun damage, it is likely that the lesion is an actinic keratosis (AK), since 37.5% of American seniors have AKs.[1] Typically, we either treat in the office or send these patients to a dermatologist for evaluation out of concern that the AK may transform into a cutaneous squamous cell carcinoma (SCC). However, recent studies have suggested that the risk of transformation is low and that active surveillance is an acceptable alternative to treatment.

AKs are premalignant lesions that develop on chronically sun-damaged skin that can either persist unchanged, regress without intervention or transform into an SCC. Historically the risk of transformation was thought to be as high as 10%, which prompted the American Academy of Dermatology to recommend treatment with either cryosurgery, topical imiquimod or topical 5-fluorouracil.[2] These treatments are relatively well tolerated, but patients can develop pain, erythema, blistering, pigment change and scarring. The economic burden of treatment is not so benign. In the 1990s, the United States spent nearly $1 billion annually on AK treatment.[3] Despite Medicare reimbursement for treatment of AK being cut in 2014, the volume of procedures continued to rise, leading to an increase in the annual cost of treatment to $1.8 billion in 2013. However, the side effects and cost of treatment were thought to be justified by the fact that 1 in 10 patients with AKs would develop SCCs.

A recent meta-analysis pertaining to AKs suggests that the annual progression rate to SCC ranges from 0% to 0.075%, not 10%, with 15%–63% regressing spontaneously within one year.[4] The small risk of progression even holds true for patients who have a history of nonmelanoma skin cancer, with the chance for progression being less than 1% in this subpopulation.[5] For those rare AKs that do transform into SCCs, only 2% subsequently metastasize, suggesting ample time for diagnosis and resection.[6] Another study has revealed that the recurrence rate for AKs at 12 or more months after treatment is similar to that seen in patients who decline an intervention.[7] Does this new understanding of the natural course of AKs still justify the risk and side effects of treatment? Does it justify the high cost in a healthcare system that is already severely strained financially? Is there a better way to approach this condition in a more patient-centered, cost-effective manner?

Active surveillance is a treatment option whereby a provider closely monitors a patient's condition but does not render treatment unless there are changes in the physical exam or surveillance tests that suggest the condition is progressing. Active surveillance has been used for years in oncology to follow low-risk prostate cancer, select papillary thyroid cancers and small kidney masses, leading to fewer unnecessary interventions while preserving the patient's quality of life.[8,9] Given that well under 1% of AKs progress to SCCs, most older patients see their PCP annually, and AKs are visible lesions that can be easily followed for progression, active surveillance should be strongly considered for this condition as well.[10]

To date, randomized clinical trials have not been performed to compare active surveillance to treatment since the low rate of progression to SCC makes such trials difficult to power adequately. However, one can apply the active surveillance protocols for low-risk basal cell carcinomas as a starting point.[11] Such a protocol would apply to immunocompetent adults with no history of skin cancer with fewer than 10 AKs, excluding lesions that are symptomatic or on the lip or eyelid. These patients could be monitored annually by their PCP and only be treated or referred to dermatology if the lesions show rapid growth. Or if the patient develops pain, ulceration or bleeding at the site.[10] Patient education is an important aspect of this strategy as many patients "expect" their AK to be treated due to current medical norms. This is an approach worth considering, to reduce low-value care, preserve our patients' quality of life and save the healthcare system close to $1 billion annually at a time when healthcare cost is front page news.

Additional benefits of GLP-1 receptor agonists for patients with type 2 diabetes mellitus — recurrent stroke prevention

Current evidence base for liraglutide and stroke

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated cardiovascular (CV) benefits in patients with high-risk type 2 diabetes (T2D). Landmark trials such as LEADER (liraglutide),[12] SUSTAIN-6 (semaglutide)[13] and REWIND (dulaglutide)[14], and recent meta-analyses (e.g., Sattar N et al., 2021)[15] reveal consistent MACE reduction across GLP-1RA agents. However, dedicated randomized clinical trials evaluating GLP-1RA efficacy in the acute ischemic stroke setting were lacking until the Liraglutide in Acute Minor Ischemic Stroke or High-Risk Transient Ischemic Attack with Type 2 Diabetes (LAMP) trial.

Key questions addressed by the LAMP trial

The LAMP trial[16] asked:

1. Is liraglutide safe and efficacious in patients with T2D and minor acute ischemic stroke (AIS) or high-risk transient ischemic attack (TIA)?
2. Does liraglutide reduce early stroke recurrence and improve functional outcomes at 90 days in this population?

Methods

The LAMP trial was a multicenter, controlled, prospective, randomized, open-label, blinded end point trial conducted at 27 hospitals in China from June 2019 through December 2023, with final follow-up on March 24, 2024. In this trial, 636 patients (median age 63.5 years; 36% female) with T2D and minor AIS (NIH Stroke Scale score ≤ 5) or high-risk TIA (ABCD² score ≥ 4) were randomized to liraglutide plus standard care versus standard care alone. The primary efficacy end point was 90-day stroke recurrence; secondary end points included functional outcome (modified Rankin Scale (mRS)).

Key findings

Within 90 days, stroke recurrence occurred in 7.9% of the liraglutide group versus 13.8% in control group (hazard ratio [HR] 0.56; 95% CI, 0.34–0.91; p = 0.02). A significantly higher proportion of patients achieved excellent functional outcomes (mRS 0–1) in the liraglutide group (87.3% vs. 77.8%, p<0.001).

Cost implications from a health system perspective

GLP-1RAs have been associated with high costs. Contemporary commentary highlights that U.S. spending on GLP-1 drugs increased over 500% since 2018, exceeding $71 billion in 2023, with semaglutide and tirzepatide accounting for $50 billion of this total.[17] Strict coverage criteria, high out-of-pocket costs and insurance premium increases have been concerns. Importantly, liraglutide's patent expired in 2024, paving the way for generic competition.[18] Generic liraglutide could lower costs, expand access and align with value-based care by providing CV benefits at lower prices. Medicaid coverage remains limited, but generic entry may improve affordability.

Implications for primary care

Results of the LAMP trial suggest potential benefit of liraglutide for stroke recurrence reduction and improved functional outcomes in patients with T2D. However, given the trial's relatively small size, findings warrant cautious interpretation and further study.

Primary care clinicians managing patients with T2D and stroke risk should note:

- GLP-1RAs (including liraglutide) provide glycemic control, weight management and CV risk reduction.
- The LAMP trial introduces the possibility of early stroke recurrence reduction.
- Value-based considerations (e.g., cost, generic availability) are important; generic liraglutide may improve access and affordability.
- Continued focus on guideline-recommended therapies for stroke secondary prevention (e.g., modifiable risk factor control, antithrombotics, statins, glucose and blood pressure control).[19] Consider GLP-1RA use for diabetes management with CV and stroke secondary prevention benefits, as per current guidelines.[20]

Use caution before prescribing aspirin for patients with chronic coronary syndrome already on oral anticoagulation

Patients with stable coronary artery disease, now called chronic coronary syndrome, are at heightened risk of acute thrombosis. Previous studies have examined the use of oral anticoagulation (OAC; e.g., apixaban, rivaroxaban) plus anti-platelet (e.g., aspirin), or anti-platelet alone. Results from the COMPASS trial support the use of dual therapy, while noting an increase in bleeding risk.[21, 22] These data support adding an OAC to anti-platelet therapy, but do not examine adding anti-platelet therapy to an OAC. A recent article in the *New England Journal of Medicine* reports on findings from the AQUATIC (Assessment of Quitting versus Using Aspirin Therapy in Patients with Stabilized Coronary Artery Disease after Stenting Who Require Long-Term Oral Anticoagulation) trial and addresses the key question:

Does adding low-dose aspirin to long-term oral anticoagulation improve outcomes in patients with chronic coronary syndrome and prior stent implantation?[23]

Methods
This prospective, multicenter, double-blind, randomized, placebo-controlled trial enrolled 872 patients in France with chronic coronary syndrome who had undergone stent implantation (> 6 months prior) and were receiving long-term oral anticoagulation. Participants were randomized to aspirin (100 mg daily) or placebo in addition to their ongoing OAC. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization or acute limb ischemia. The key safety outcome was major bleeding. Median follow-up was 2.2 years; the trial was terminated early due to excess mortality in the aspirin group.

Key findings
Adding aspirin increased cardiovascular events, mortality and bleeding risk without benefit. Outcome for the aspirin group is listed first, compared with the placebo group.

- Primary composite outcome: 73 patients (16.9% (aspirin)) vs. 53 patients (12.1% (placebo)); HR 1.53 (95% CI, 1.07–2.18; p=0.02).
- All-cause mortality: 58 (13.4%) vs. 37 (8.4%); HR 1.72 (95% CI, 1.14–2.58; p=0.01).
- Major bleeding: 44 (10.2%) vs. 15 (3.4%); HR 3.35 (95% CI, 1.87–6.00; p<0.001).

Implications for primary care
Based on these results, avoiding adding aspirin to oral anticoagulation in patients with chronic coronary syndrome post-stenting may be advised. Dual therapy in this context may be harmful. Individualize antithrombotic regimens, prioritize safety and use shared decision-making. Findings and recommendations comport with ACC/AHA guidelines for patients on OAC and no other indications for aspirin use.[24]

With atrial fibrillation, no need to hold off on having a cappuccino

Conventional wisdom is that caffeine consumption can cause cardiac rhythm irritability and potentially trigger bouts of atrial fibrillation (AF) or atrial flutter in those susceptible. The DECAF trial examined the key question:[25]

Does caffeinated coffee consumption versus abstinence affect recurrent AF or atrial flutter in patients undergoing cardioversion?

Methods
The authors describe a prospective, open-label, international, multicenter study enrolling 200 adults with persistent AF or atrial flutter who were current or recent coffee drinkers. Participants were randomized 1:1 to consume caffeinated coffee (≥ 1 cup/day) or abstain from all caffeine for 6 months. The primary outcome was clinically detected recurrence of AF or atrial flutter.

Key findings
Coffee consumption was associated with a lower recurrence rate (47%) compared with abstinence (64%), corresponding to a 39% lower hazard of recurrence (HR 0.61; 95% CI, 0.42–0.89; p = 0.01). No significant differences in adverse events were observed. Baseline coffee intake averaged 7 cups per week in both groups; during follow-up, consumption averaged 7 versus zero cups per week. These findings comport with a previous meta-analysis of studies examining caffeine consumption and risk of AF.[26]

Implications for primary care
These findings challenge conventional wisdom that caffeine is proarrhythmic and should be avoided in patients with AF. Clinicians may reconsider recommending blanket coffee abstinence, particularly for patients who prefer coffee, as moderate consumption appears safe and potentially beneficial.

23-year follow-up of seminal study on PSA screening and mortality — patient-specific approach still advised

Prostate-specific antigen (PSA) screening remains controversial due to modest mortality benefits and significant risks of overdiagnosis and overtreatment. The European Randomized Study of Screening for Prostate Cancer (ERSPC) is considered the only study to establish a benefit of screening. Roobol et al. recently published a 23-year follow-up of the study population.[27] Previous ERSPC reports demonstrated a relative reduction in prostate cancer mortality but with associated high numbers needed to invite (NNI) for screening and numbers needed to diagnose (NND). [28,29] The 23-year follow-up further updates the numbers from previous analyses.

Methods
The ERSPC is a multicenter, randomized trial across 8 European countries, enrolling 162,236 men aged 55–69 years that started in 1993. Participants were randomized to repeated invitation for PSA screening or no screening invitation. In the current report, the primary outcome was prostate cancer mortality assessed after a median follow-up of 23 years.

Key findings

- Prostate cancer mortality was 13% lower in the invite-for-screening group (rate ratio 0.87; 95% CI, 0.80–0.95).
- Risk of death from prostate cancer at 23 years from the start of the study was 1.4% in the invite-for-screening group versus 1.6% in the control group
  - Absolute risk reduction: 0.22% (95% CI, 0.10–0.34).
- One prostate cancer death prevented per 456 men invited.
- Overdiagnosis persists; cumulative incidence was 30% higher in the screening group. The risk ratios comparing those invited for screening versus not invited are as follows:
  - Low-risk prostate cancer diagnosis 2.14 (95% CI, 2.04 – 2.25),
  - Intermediate risk 1.10 (95% CI, 1.04 – 1.17),
  - High risk 0.95 (95% CI, 0.89 – 1.01),
  - Advanced prostate cancer 0.66 (95% CI, 0.60 – 0.74)
- One death was averted for every 12 men diagnosed and treated.
- Long-term follow-up confirms sustained mortality benefit with an improved harm-benefit ratio, though absolute benefit remains modest.

Cost implications
While direct cost data are not reported, the high NNI/NND and increased incidence of low-risk disease suggest that population-wide screening remains unlikely to be cost-effective. A value-based approach favors risk-stratified screening, targeting men most likely to benefit and avoiding screening in older cohorts (> 70 years), consistent with USPSTF recommendations (Grade D for men > 69).[30]

Implications for primary care
Primary care clinicians should engage patients in informed discussions about PSA screening, weighing individual risk factors, life expectancy and patient preferences. A value-based lens supports selective, risk-adapted screening with subsequent targeted image-guided biopsies when indicated to maximize benefit, minimize harm from overdiagnosis and control unwarranted costs.

Single-dose HPV vaccination and cervical HPV infection: Evidence and implications for primary care

Recent evidence from the ESCUDDO randomized trial further demonstrates that a single dose of either bivalent or nonavalent HPV vaccine is noninferior to 2 doses in preventing persistent HPV16/18 infection, the primary cause of cervical cancer.[31] This builds on prior immunogenicity and efficacy studies and aligns with WHO's 2022 recommendation for one or two doses for girls and women up to age 20 years.[32] Over 80 countries have adopted single-dose regimens, supported by data showing durable protection for at least 5 years. The ESCUDDO trial addressed the following key question:

Is one HPV vaccine dose noninferior to two doses in preventing new HPV16/18 infections persisting ≥ 6 months?

Methods
In an open-label, randomized design, 20,330 females aged 12–16 years in Costa Rica were assigned to one or two doses of bivalent or nonavalent vaccine. The primary end point was infection incidence from months 12–60 (5 years), with a prespecified noninferiority margin of 1.25 infections per 100 participants. Outcomes were compared with an unvaccinated survey cohort of 3,005 females aged 16–21 years. Based on the statistical approach used, if the upper bound of the 95% confidence interval was less than or equal to 1.25 infections per 100 participants, the null hypothesis of inferiority would be rejected at a one-sided significance level of 0.025.

Key findings
One dose was noninferior to two doses: the rate difference was -0.13 infections per 100 participants (95% confidence interval CI, -0.45 to 0.15; $p<0.001$ for noninferiority) for bivalent vaccine. What this means is that every 100 participants who received one dose of the vaccine had 0.13 fewer infections within 5 years after vaccination than those who received 2 doses. For the nonavalent vaccine, rate difference was 0.21 infections per 100 participants (95% CI, -0.09 to 0.51; $p<0.001$ for noninferiority). Vaccine effectiveness in preventing HPV16 or HPV18 infection that persisted for at least 6 months exceeded 97% across groups, with no safety concerns. The accompanying editorial underscores that single-dose efficacy meets the surrogate end point for cervical cancer prevention.[33]

Caveats
Long-term immunity beyond 5 years has not yet been established. CDC currently recommends a 2-dose regimen.[34, 35]

Implications for primary care
Findings align with WHO guidance endorsing one or two doses for adolescents and young women. Primary care clinicians should prioritize HPV vaccination during routine visits, advocate for catch-up programs and educate families on the effectiveness and safety of the vaccine. Simplified schedules can improve adherence and expand access, advancing the goal of cervical cancer elimination.

Melanoma in situ overdiagnosis may also lead to overtreatment

There have been several concerns raised about melanoma in situ (MIS) overdiagnosis. Patel et al. found low mortality risk after MIS diagnosis.[36] Sun et al. reported low recurrence for small MIS excised with 5-mm margins.[37] One consequence of overdiagnosis is overtreatment. Dessinioti et al. recently reported results from a study that addresses the key question:

Is wide excision after initial excisional biopsy necessary for non-lentigo maligna (non-LM) and non-acral lentiginous (non-ALM) MIS to prevent recurrence, metastasis or melanoma-related death?[38]

Methods
Authors performed a retrospective analysis of a cohort of 401 patients (403 lesions) treated at a single center in Athens, Greece (1991–2023). All lesions underwent excisional biopsy; 92.3% had subsequent wide excision. Patients with prior invasive melanoma or LM/ALM MIS were excluded. Outcomes included local recurrence, metastasis and melanoma-specific survival over a median follow-up of 5.2 years (range up to 26 years).

Key findings

- 97.9% of lesions achieved clear margins after excisional biopsy.
- Only one local recurrence occurred — in a patient with involved margins who did not undergo wide excision.
- 30 lesions with clear margins and without wide excision showed no recurrence at a median follow-up of 8.1 years.
- 23 lesions excised with margins narrower than the standard 0.5 cm had no recurrences at a median follow-up of 4.3 years.
- No metastases or melanoma-specific deaths were observed.
- Melanoma in situ overdiagnosis may also lead to overtreatment.

Caveats
The study's retrospective, single-center design and exclusion of LM/ALM subtypes limit generalizability. Current guidelines still recommend biopsy and subsequent excision of at least 5 mm for MIS, regardless of initial margin status.[39,40]

Implications for primary care
For non-LM/non-ALM MIS with clear excisional margins, additional wide excision may offer limited benefit. Clinicians should consider individualized surgical planning and shared decision-making, balancing guideline adherence with emerging evidence to avoid overtreatment. Patients can be reassured about the very low risk of recurrence, metastasis and death when MIS is adequately excised. In select cases, fewer surgical interventions may reduce morbidity, psychological burden and resource overutilization.

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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 is now part of Optum Care. He served as chief medical officer from 1995 to 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 American Medical Group Association 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.

Scott Hines, MD

Chief Quality Officer, Optum NY/NJ; Chief Clinical Standards Officer, Optum East Endocrinologist

Dr. Scott Hines is a board-certified endocrinologist who has held multiple executive leadership roles with Crystal Run Healthcare and Optum Health since 2006, including Medical Director of Medical Specialties, Chief Quality Officer and Chief Clinical Standards Officer. In these roles, Scott helped to develop and implement the clinical programs necessary to deliver value-based care such as best practice guidelines, a variation reduction program and various quality improvement initiatives. Dr. Hines is also well known regionally and nationally for his work related to value-based care. Scott has delivered multiple presentations highlighting Crystal Run's value journey for various national organizations including the American Medical Group Association (AMGA), Brookings Institution, ACO World Conference and the Group Practice Improvement Network (GPIN). Scott was a previous board member for AMGA, is the current chair of AMGA's Public Policy Committee and was a past chair of AMGA's Quality Council.

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