Letters to the Editor

Further Discussion Regarding Multicancer Early Detection Tests

To the Editor: We would like to comment on several statements in the editorial on multicancer early detection tests by Drs. Doubeni and Castle.[1]

The editorial states that performance characteristics of these tests are unclear for people in primary care. Two studies assessed multicancer early detection tests in average-risk populations: the PATHFINDER study in 6,662 asymptomatic adults and the DETECT-A study in 10,000 women.[2,3] PATHFINDER reported a specificity of 99.5% and a positive predictive value of 43%.[2] The DETECT-A study, based on two blood tests, reported a specificity of 98.9% and a positive predictive value of 19.4%.[3]

Furthermore, the editorial states that multicancer early detection tests have not been studied to distinguish indolent from lethal lesions. A study by Chen, et. al, showed that one of two prospectively studied multicancer early detection tests preferentially detects aggressive cancers.[4]

The editorial continues by stating that individual cancers are rare and that most people undergoing screening will not benefit and are at risk of potential harms. This highlights the statistical value of multicancer early detection tests: the utilization of aggregate prevalence. Tests for multiple cancers have a lower number needed to screen and a higher positive predictive value than a screening test for a single cancer type.[5]

The editorial states that screening and detection during the occult preclinical phase can create an illusion of longer survival. Lead-time bias is addressed by randomized controlled trials such as the ongoing NHS-Galleri trial, which includes more than 140,000 patients.[6]

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Author disclosure: Dr. Raoof reports serving as a speaker, consultant, or advisory board member for Verily Life Sciences, Exact Sciences, GRAIL, GLG, PRIMED, and AstraZeneca. Dr. Klein reports current employment with GRAIL.

Email letter submissions to afplet@aafp.org. Letters should be fewer than 400 words and limited to six references, one table or figure, and three authors. Letters submitted for publication in *AFP* must not be submitted to any other publication. Letters may be edited to meet style and space requirements.

This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

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In Reply: We thank Drs. Raoof and Klein for their comments. The PATHFINDER and DETECT-A studies were feasibility investigations and not designed for accurately assessing sensitivity and specificity.[1,2] Sensitivity and specificity determinations require establishing the presence or absence of cancer with a gold standard test administered to all participants at the same time as the multicancer early detection test, which neither study did.[1] In both studies, differential verification, selection, or spectrum biases would overestimate test accuracy and limit generalizability.[3,4] The PATHFINDER study included people with hereditary cancer predisposition and history of cancer; therefore, positive predictive values would be lower in a general screening population than inferred from that study. The sample was also fairly homogeneous (92% White participants). These studies are useful for establishing feasibility but unsuitable for establishing accuracy or clinical utility in primary care.

Tests with high specificity tend to have high false-negative rates. The sensitivity reported for CANCERSEEK in the DETECT-A study was 27%.[2] Current multicancer early detection tests have lower sensitivity for earlier-stage cancers, which are the main targets of screening. Differentiating cancer precursors or early cancers that will be fatal in a person's lifetime from indolent lesions that are nonfatal is the goal of clinical prevention.[5] Those questions cannot be answered by a study such as Chen, et al., that used previously diagnosed cancer cases.

Screening in clinical prevention is a series of care processes that extend beyond performing the test.[4] Although combining outcomes across all detectable cancers could yield higher statistical power for a given sample, the effectiveness of screening is not based solely on the ability to detect cancer, but on the ability to prevent premature

death from cancer.[6] For some cancers (i.e., ovarian cancer and pancreatic cancer), studies have shown that screening results in net harm or does not demonstrate a mortality benefit. Multicancer early detection tests should be studied to demonstrate the ability to decrease the risk of dying from an individual cancer or multiple cancers.[1]

We agree that randomized controlled trials are the ideal to demonstrate whether multicancer early detection tests provide more benefits than harms, and we look forward to the results of the NHS-Galleri study and others. Such studies should be designed and powered to show the effect on mortality and the harms of testing, and need many years of follow-up. We need such evidence to support using multicancer early detection tests in routine screening of asymptomatic people.[1]

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Low-Dose Naltrexone: A Possible Option for Fibromyalgia

To the Editor: We want to thank Dr. Winslow and colleagues for their excellent review of fibromyalgia.[1] A patient recently presented to our practice who was taking recommended medications for fibromyalgia without much relief. The patient approached us about using low-dose naltrexone (Revia). A PubMed search showed that low-dose naltrexone (1 to 5 mg) has been used off-label to treat inflammation and pain in fibromyalgia, multiple sclerosis, and Crohn disease.[2] The mechanism of action is the modulation of neuroinflammation, specifically, the release of inflammatory chemicals in the central nervous system and the modulation of glial cells.[3] Randomized, placebo-controlled trials are being conducted to add more data to the literature.[4,5] Although low-dose naltrexone shows promise in relieving pain symptoms for people with fibromyalgia, a challenge is its limited availability. Currently, oral naltrexone is available only in 50-mg tablets. Compounding pharmacies may be able to create low-dose naltrexone, but insurance coverage presents another challenge. After discussing the potential benefits and risks, the patient decided to try one-half of the 50-mg tablet and found some relief.

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Author disclosure: No relevant financial relationships.

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Editor's Note: This letter was sent to the authors of "Fibromyalgia: Diagnosis and Management," who declined to reply.

Corrections

Incorrect Grading Scale. In the article "Bell Palsy: Rapid Evidence Review" (April 2023, p. 415), one of the grades in the House-Brackman scale for classifying symptom severity of Bell palsy was inadvertently omitted in the right column of page 416. The last two grades should have read as follows:

- Grade V, severe symptoms: only slight, barely noticeable facial movement, asymmetric facial appearance, forehead cannot move, incomplete eyelid closure, mouth has only slight movement.
- Grade VI, total paralysis: no facial movement.

The online version of this article has been corrected.

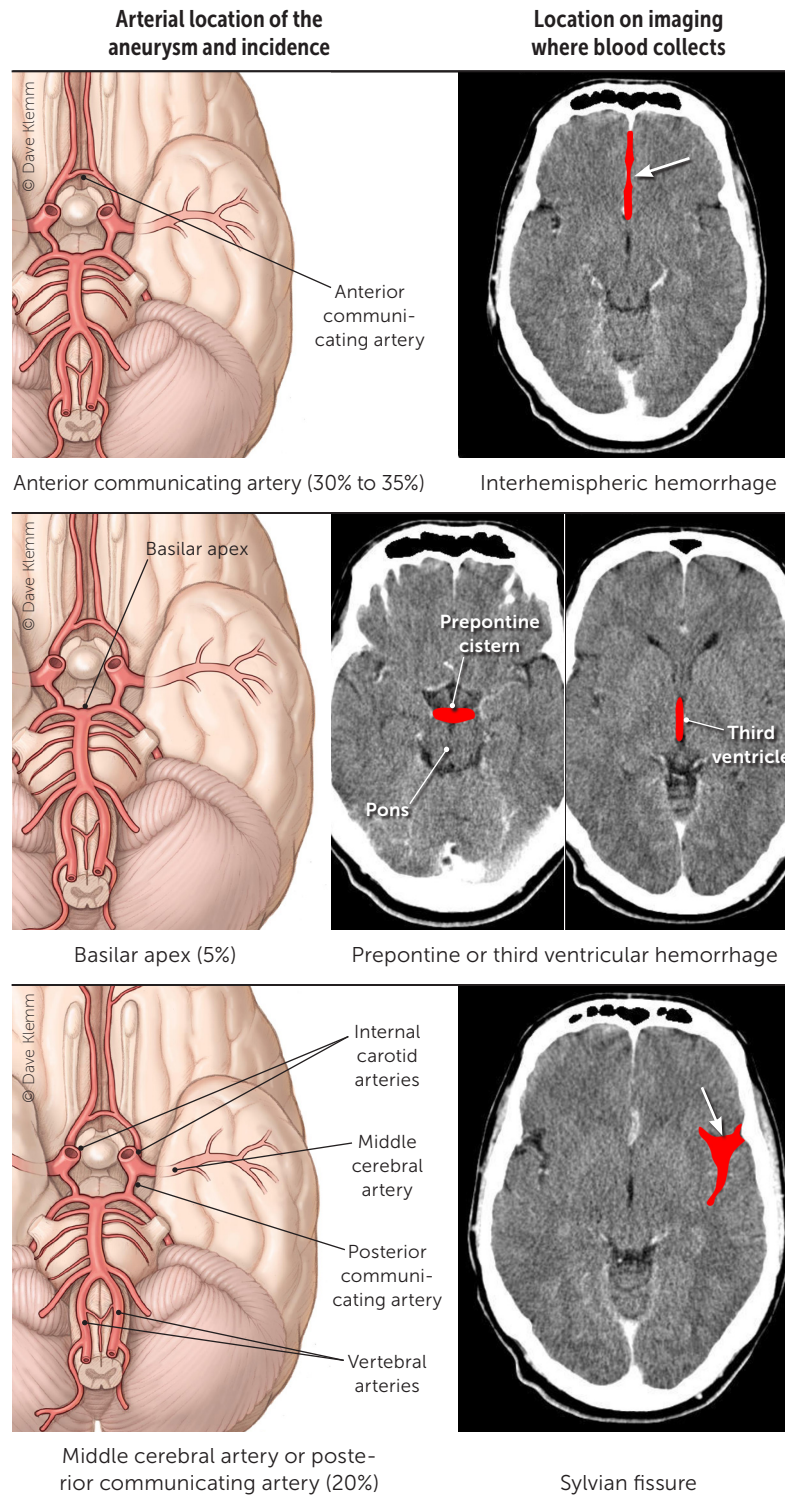
Table Columns Switched. In the article "Growth Faltering and Failure to Thrive in Children" (June 2023, p. 597), the information in the "Water (oz)" and "Formula" columns was inadvertently switched in the "Liquid Formula" section of

Table 4 (p. 601). Also, in the last sentence of the first paragraph of the Diagnosis section (p. 598), Bell palsy was inadvertently listed instead of cerebral palsy. The sentence should have read, "Adjusted growth charts are available for children with conditions such as cerebral palsy, Down syndrome, Turner syndrome, and cri du chat syndrome, but these are based on smaller data samples." The online version of the article has been corrected.

Incorrect Statistic. In the article "Preventing CVD in Women: Common Questions and Answers" (December 2023, p. 595), the numbers of cardiovascular events occurring in relation to age at onset of menopause were inadvertently listed in the wrong order in the first paragraph of the Evidence Summary in the Menstrual Characteristics section (p. 597). The second sentence of the paragraph should have read, "Compared with menopause onset at 55 years or older, CVD events occur more often in those who have an earlier onset, with 2.6 events per 1,000 person-years for onset at 45 to 49 years of age, 3 events per 1,000 person-years for onset at 40 to 45 years of age, and 4 events per 1,000 person-years for onset before 40 years of age." The online version of the article has been corrected.

Misplaced Figures. In the article "Nontraumatic Subarachnoid Hemorrhage and Ruptured Intracranial Aneurysm: Recognition and Evaluation" (October 2023, p. 386), the images in the left column of Figure 2 (p. 389) were placed incorrectly, resulting in the accompanying figure legends being placed by the wrong images. Figure 2 is reprinted here, and the online version of the article has been corrected. ■

FIGURE 2



Common locations of intracranial aneurysms with approximate incidence and location on imaging where blood collects.

Illustrations by Dave Klemm.

Information from references 16, 17, and 21.