the public is seeking high-quality care. Greater integration of services is essential to addressing the issue of quality. In the physician-assistant community, we call it team practice. The health care system long ago moved beyond the model of the solo practitioner as the ideal way to deliver health care. Today, all practitioners, including physicians, are integrated through an intricate network of referrals, review systems, and shared information systems.

The question of whether greater use of nonphysicians results in a growing coordination or fragmentation of care can be answered by studying the team practice of physicians and physician assistants. It is increasingly necessary that we evaluate the role, function, and effects of team practice, rather than focus on the contributions of individual clinicians who are presumably acting alone.

The article by Druss et al. answers the question of who provides health care. Research is still needed to answer the question of how medical care, provided by a team of clinicians under the leadership of a physician, is coordinated in actual practice and how society can use this method to ensure appropriate access to high-quality care.

Stephen C. Crane, Ph.D., M.P.H.

American Academy of Physician Assistants
Alexandria, VA 22314-1552

1. Druss BG, Marcus SC, Olfson M, Tanielian T, Pincus HA. Trends in care by nonphysician clinicians in the United States. N Engl J Med 2003;348:130-7.

DR. DRUSS REPLIES: I appreciate both the content and the spirit of Dr. Crane's letter. I agree that the study points to a need for a better understanding of how medical care is and, more important, should be coordinated among the many groups of clinicians that provide it. It is essential that these efforts themselves be both multidisciplinary and collaborative.

Benjamin Druss, M.D., M.P.H.

Emory University
Atlanta, GA 30322
bdruss@sph.emory.edu

Population Screening

TO THE EDITOR: In their review article, Khoury et al. (Jan. 2 issue)[1] suggest that homocystinuria should be screened for by Guthrie bacterial inhibition assay and treated with vitamin B_{12} and methionine restriction. Homocystinuria occurs in several conditions, including cystathionine β-synthase deficiency and genetic disorders of homocysteine remethylation.[2,3] Plasma total homocysteine levels may also be elevated because of folate deficiency or vitamin B_{12} deficiency.[2] The Guthrie test, designed to detect hypermethioninemia, fails to detect abnormalities of homocysteine remethylation. Hypermethioninemia occurs not only in cystathionine β-synthase deficiency but also in a variety of other conditions.[2,4,5] Cystathionine β-synthase deficiency is readily differentiated from other disorders, since either plasma cystathionine will not be detected at all or the level will be very low in patients with this deficiency, whereas the level will be normal or elevated in patients with other conditions causing elevated methionine or total homocysteine levels.[5]

Methionine restriction may be therapeutic in cystathionine β-synthase deficiency but not in the latter conditions. Patients with such a deficiency may have a response to vitamin B_6. Methionine restriction and betaine are used in patients without a response to vitamin B_6. Vitamin B_{12} and folate are sometimes used as adjuvant therapy.[2] Vitamin B_{12} is specifically indicated for disorders affecting methylcobalamin synthesis.[3] Diagnosis and treatment of cystathionine β-synthase deficiency and errors affecting the homocysteine remethylation may prevent mental retardation and thromboembolic episodes. We recommend that disorders of methionine and homocysteine metabolism be classified according to the specific causative deficiency of enzyme activity or vitamin and that concurrent assays of plasma total homocysteine, cystathionine, and methionine be performed. Methylmalonate should be measured if disorders related to cobalamin are suspected. Assays of plasma S-adenosylmethionine and sarcosine can be performed for the rarer inborn errors.

Sally P. Stabler, M.D.

University of Colorado Health Sciences Center
Denver, CO 80262
sally.stabler@uchsc.edu

S. Harvey Mudd, M.D.

National Institute of Mental Health
Bethesda, MD 20892

Editor's note: The University of Colorado and Dr. Stabler hold patents on the use of homocysteine, cystathionine, and methylmalonic acid in the diagnosis of folate deficiency and vitamin B_{12} deficiency. A company has been formed at the University of

Colorado to perform the assays. Dr. Stabler holds patents on combination vitamin treatment of homocysteine.

1. Khoury MJ, McCabe LL, McCabe ERB. Population screening in the age of genomic medicine. N Engl J Med 2003;348:50-8.
2. Mudd SH, Levy HL, Kraus JP. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic & molecular bases of inherited disease. 8th ed. Vol. 2. New York: McGraw-Hill, 2001:2007-56.
3. Rosenblatt DS, Fenton WA. Inherited disorders of folate and cobalamin transport and metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic & molecular bases of inherited disease. 8th ed. Vol. 3. New York: McGraw-Hill, 2001:3897-933.
4. Mudd SH, Cerone R, Schiaffino MC, et al. Glycine N-methyltransferase deficiency: a novel inborn error causing persistent isolated hypermethioninaemia. J Inherit Metab Dis 2001;24:448-64.
5. Stabler SP, Steegborn C, Wahl MC, et al. Elevated plasma total homocysteine in severe methionine adenosyltransferase I/III deficiency. Metabolism 2002;51:981-8.

TO THE EDITOR: The article by Khoury et al. missed several important points. The first principle set forth by Wilson and Jungner[1] mandates that screening should be undertaken only for health problems that are important in terms of both the severity of disease and its frequency at the level of public health. Most monogenic disorders do not qualify in terms of frequency.

Fear of disease by laypersons, a defensive medicolegal culture, and a weakly regulated marketplace mean that purveyors of "at risk" testing will proliferate, resulting in unforeseen social and psychological harms. Once genetic variants are identified, what then?

Correctly recognizing that tandem mass spectrometry identifies many conditions for which no treatment, clear understanding of appropriate management, or preventive strategies exists, the authors justify this technique on the basis that it can help to eliminate the need for "diagnostic odysseys" if low-probability health problems emerge. They fail to mention that tandem mass spectrometry and similar methods for mass genetic screening almost guarantee an epidemic of therapeutic odysseys, as anxious parents seek multiple treatments for diseases that may never become symptomatic. We should not allow the potential hazards and costs of genetic screening to remain as underemphasized as they were in the article by Khoury et al.

Richard Fielding, Ph.D.
Wendy Lam, Ph.D.
Gabriel M. Leung, Ph.D.

University of Hong Kong
Hong Kong, China
fielding@hkusua.hku.hk

1. Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Pap 1968;34:11-163.

THE AUTHORS REPLY: We agree with Stabler and Mudd that the screening of newborns for hypermethioninemia will identify only a subgroup of patients with homocystinuria and will identify patients who have hypermethioninemia for other reasons, including liver disease. The challenge for those desiring more comprehensive ascertainment of inborn errors of metabolism is to develop technological approaches that will be able to accommodate high sample throughput in a cost-effective manner.[1,2] The application of tandem mass spectrometry to the screening of newborns offers detection to a much larger group of infants with specific inborn errors of metabolism than was previously possible.

Fielding et al. raise important issues regarding the selection of diseases for population-based screening. All 50 states and the District of Columbia have determined that newborn screening programs represent an important investment for the prevention of death and disability.[3] These are decisions that must be made openly, with full representation of professionals and the public. The costs of investment in new technologies such as tandem mass spectrometry must be considered carefully.

Population screening requires assessment of the goals for the program and ongoing evaluation to ensure that its goals are being achieved. We appreciate the opportunity to expand the dialogue about screening.

Muin J. Khoury, M.D., Ph.D.

Centers for Disease Control and Prevention
Atlanta, GA 30333

Linda L. McCabe, Ph.D.
Edward R.B. McCabe, M.D., Ph.D.

David Geffen School of Medicine at UCLA
Los Angeles, CA 90095-1752
emccabe@mednet.ucla.edu

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3. Serving the family from birth to the medical home: newborn screening: a blueprint for the future — a call for a national agenda on state newborn screening programs. Pediatrics 2000;106:389-422.