ning. Patients assigned to CAC had improvements in blood pressure (P=0.02), cholesterol levels (P=0.04), waist circumference (P=0.01), and Framingham risk score (P=0.003) as compared with those assigned to no scanning.

The patient described by Grayburn was reclassified with the use of the CAC score, and the treatment (adding aspirin and increasing the dose of rosuvastatin) was prudent and appropriate.

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No potential conflict of interest relevant to this letter was reported.

1. Grayburn PA. Interpreting the coronary-artery calcium score. N Engl J Med 2012;366:294-6.
2. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56(25):e50-e103.
3. Villines TC, Hulten EA, Shaw LJ, et al. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry. J Am Coll Cardiol 2011;58:2533-40.
4. Arad Y, Spadaro LA, Roth M, Newstein D, Guerci AD. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol 2005;46:166-72. [Erratum, J Am Coll Cardiol 2011;58:1832.]
5. Rozanski A, Gransar H, Shaw LJ, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing: the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol 2011;57:1622-32.

THE AUTHOR REPLIES: A review of imaging guidelines for asymptomatic CAD showed that 11 of 14 guidelines support the use of CAC scoring in intermediate-risk patients.[1] The updated appropriate-use criteria state that this indication assumes that CAC scoring is done by "competent and appropriately credentialed physicians."[2] I believe that competence should include clinical application and patient counseling, not merely interpretation of scans.

Regardless of symptoms, CAD may be present without CAC. This point warrants emphasis even though CAC scoring "had a negative predictive value of 99% for greater than 70% stenosis." First, acute myocardial infarction often occurs at sites of less than 50% stenosis.[3] Second, symptoms are notoriously misleading in acute myocardial infarction. In a recent observational study involving more than 1 million patients who were hospitalized with acute myocardial infarction, 42% of women and 31% of men did not have chest pain[4]; this was most pronounced in younger women, in whom CAC may be absent.

My specific comment was that "there have been no prospective, randomized, controlled trials demonstrating that an abnormal CAC score influences treatment decisions or outcomes." The St. Francis and EISNER studies, though valuable contributions to the literature, were not designed to answer that difficult but important question.

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Since publication of his article, the author reports no further potential conflict of interest.

1. Ferket BS, Genders TSS, Colkesen EB, et al. Systematic review of guidelines on imaging of asymptomatic coronary artery disease. J Am Coll Cardiol 2011;57:1591-600.
2. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. J Am Coll Cardiol 2010;56:1864-94.
3. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35. [Erratum, N Engl J Med 2011;365:2040.]
4. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA 2012;307:813-22.

Pulmonary Fibrosis, Bone Marrow Failure, and Telomerase Mutation

TO THE EDITOR: Telomeres protect the ends of chromosomes from erosion; telomerase ensures their integrity.[1,2] We report a case of familial idiopathic pulmonary fibrosis and bone marrow failure associated with a mutation in telomerase reverse transcriptase (*TERT*).

The patient was a 56-year-old lifelong nonsmoker with hyperlipidemia, type 2 diabetes mellitus, treated vitamin B_{12} deficiency, and mild pancytopenia. He had received a diagnosis of idiopathic pulmonary fibrosis at 49 years of age. Pulmonary-function testing 2 months before admission revealed a severe restrictive ventilatory defect and decreased diffusing capacity (see Ta-

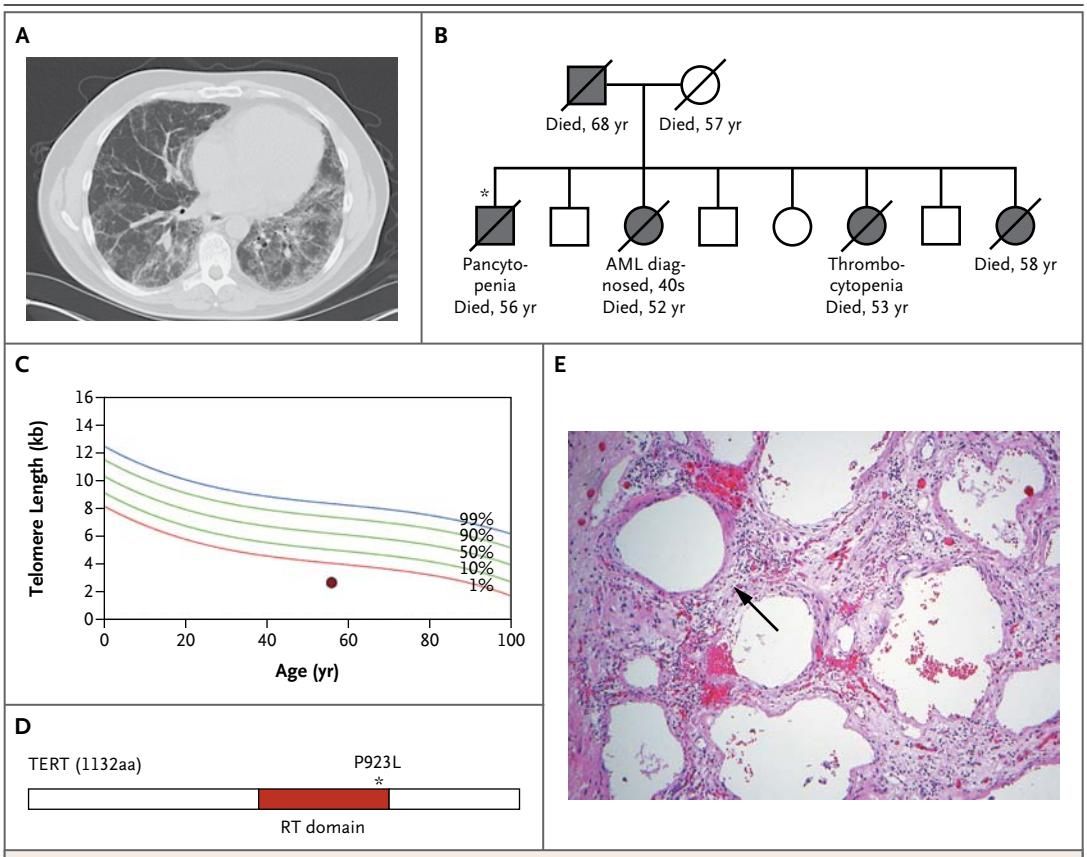

Figure 1. Familial Idiopathic Pulmonary Fibrosis and Bone Marrow Failure Associated with a New Mutation in Telomerase Reverse Transcriptase (*TERT*).

Panel A shows a computed tomographic scan of the patient's chest obtained 2 months before admission. Diffuse interstitial lung disease with peripheral and basilar distribution associated with honeycombing and bronchiolectasis is shown. Panel B shows the family pedigree. Squares indicate male family members, and circles female family members. Shading indicates patients with confirmed or presumed idiopathic pulmonary fibrosis. Deceased family members are indicated by slashes through the symbols, and the asterisk indicates the index patient. AML denotes acute myeloid leukemia. Panel C shows the median telomere length in lymphocytes measured by means of flow fluorescence in situ hybridization. In this patient (data point), this length was less than the first percentile for age. Panel D shows the location of the P923L substitution in TERT (asterisk). Red indicates the reverse transcriptase (RT) domain. Panel E shows an autopsy specimen of the lung indicating severe fibrosis (arrow).

ble 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org); computed tomography showed interstitial lung disease (Fig. 1A).

The patient had a large family (Fig. 1B). His father had pulmonary fibrosis that was confirmed by means of biopsy. One sister died of idiopathic pulmonary fibrosis. A second sister had thrombocytopenia and idiopathic pulmonary fibrosis that was confirmed at autopsy. A third sister had idiopathic pulmonary fibrosis and died from acute myeloid leukemia.

Laboratory values included a white-cell count of 3.6 per cubic millimeter, a hemoglobin level of 11.1 g per deciliter, a platelet count of 82 per cubic millimeter, and a vitamin B_{12} level of 519 pg per milliliter (see Table 2 in the Supplementary Appendix).

The patient's bone marrow was moderately hypocellular (30% cellularity). Telomere lengths in lymphocytes (Fig. 1C) and granulocytes were less than the first percentile for age, a finding most consistent with an underlying telomerase complex mutation.[3] Gene sequencing confirmed a heterozygous mutation in *TERT*, c:2768C→T, which causes a substitution of leucine for proline at amino acid 923 (Fig. 1D). This proline is conserved in all vertebrate species that we have examined and is located within a putative oligomerization domain (Fig. 1 in the Supplementary

Appendix).[4] No variants at this position are indicated in the National Center for Biotechnology Information dbSNP database. Furthermore, in silico analysis with the use of the SNPs3D database suggests that the P923L substitution is functionally deleterious.

The patient's respiratory status declined precipitously; he died of treatment-refractory hypoxemia. An autopsy confirmed severe, diffuse pulmonary fibrosis (Fig. 1E) with the presence of honeycomb changes at the lung bases.

This case illustrates some of the pleiotropic effects of telomerase dysfunction and shows the clinical significance of the TERT P923L mutation. It supports the observation of genetic anticipation in families with telomerase mutations and highlights the importance of taking a family history that is not limited to a single organ system. Most patients with idiopathic pulmonary fibrosis are considered for lung transplantation; it will thus be important to determine whether telomerase mutations alter outcomes for lung-transplant recipients and whether tandem lung–bone marrow transplantation benefits a subgroup of these patients. Clinicians should be alert for telomerase mutations in patients who present with idiopathic pulmonary fibrosis and pancytopenia.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Calado RT, Young NS. Telomere maintenance and human bone marrow failure. Blood 2008;111:4446-55.
2. Armanios M. Syndromes of telomere shortening. Annu Rev Genomics Hum Genet 2009;10:45-61.
3. Alder JK, Chen JJ, Lancaster L, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A 2008;105:13051-6.
4. Arai K, Masutomi K, Khurts S, Kaneko S, Kobayashi K, Murakami S. Two independent regions of human telomerase reverse transcriptase are important for its oligomerization and telomerase activity. J Biol Chem 2002;277:8538-44.

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Contact Melissa Brennan, Boston University School of Medicine, 771 Albany St., Suite 3509, Boston, MA 02118; or call (617) 414-7424; or fax (617) 414-3833; or e-mail melissa.brennan@bmc.org.

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The conference of the Association for Medical Education and Research in Substance Abuse will be held in Bethesda, MD, Nov. 1–3. Deadline for submission of travel award applications is May 4. Deadline for submission of abstracts and workshops is May 25.

Contact the Association for Medical Education and Research in Substance Abuse, P.O. Box 20160, Cranston, RI 02920; or e-mail doreen@amersa.org; or see http://www.amersa.org.

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