

ibration) rates when added to conventional risk factors.¹

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Drs. Gulcher and Stefansson report having financial interest in their own company, Decode Genetics, which markets a genetic-risk test for type 2 diabetes that includes some of the genetic markers reported in the article by Lyssenko et al. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: In response to Narayan and Weber: although there is sufficient knowledge to initiate translational studies aimed at prevention of type 2 diabetes, this does not mean that we should not continue to identify genetic variants that increase susceptibility to the disease. The use of such variants for identifying people who are at increased risk for disease is only one goal.

We should not underestimate the importance of identifying novel pathogenic pathways.¹ The strongest type 2 diabetes gene, *TCF7L2*, was unknown until genetic research provided this finding in 2006.² *TCF7L2* might be an important link between incretins and islet function.³ Recently, common variants in the gene encoding the melatonin receptor 1B (*MTNR1B*) have been associated with an increased risk of type 2 diabetes.⁴ Time will show whether this finding can explain the well-known link between sleep disturbances and type 2 diabetes.

We agree with Gulcher and Stefansson that

an improvement in the reclassification of 15.6% of subjects is not trivial. The main reason for our cautious conclusion is that we have not yet been able to explain why the relative risk of type 2 diabetes among persons with a family history of the disease is approximately three times higher than it is among persons without a family history of the disease.⁵ Genetic markers clearly performed better the earlier they were tested, and it is not surprising that they do not add much to a clinical prediction that is based on measures used to define the outcome (e.g., the glucose level). We completely agree that it is unlikely that the risk will be identical for all genetic markers. Unfortunately, existing methods for analyzing data have not been optimal, and we need to develop better methods for assessing the genetic risk of a complex disease.

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PHD2 Mutation and Congenital Erythrocytosis with Paraganglioma

TO THE EDITOR: Ladroue et al. (Dec. 18 issue)¹ describe a patient with a newly discovered mutation of the gene encoding prolyl hydroxylase domain 2 (*PHD2*). In addition to erythrocytosis, this patient had recurrent abdominal tumors. The authors state that the *PHD2* mutation affects the stability and functions of hypoxia-inducible factor (HIF) and that prolyl hydroxylase (PHD) inhibitors should be evaluated for an oncogenic effect. We think that the way in which PHD functions affect oncogenesis remains unclear. For example,

did the authors detect elevated levels of HIF-1 α or HIF-2 α in the tumor in this patient? Do the authors have evidence that the *PHD2* mutation stabilized HIF in this patient?

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and congenital erythrocytosis with paraganglioma. *N Engl J Med* 2008;359:2685-92.

THE AUTHORS REPLY: We agree with Eltzschig et al. that the mechanisms underlying the role of PHD proteins in oncogenesis remain unclear. Nonetheless, a link between the inhibition of PHD proteins due to the accumulation of Krebs-cycle intermediates and the occurrence of tumors in patients with germ-line fumarate hydratase (*FH*) and succinate dehydrogenase (*SDH*) mutations has been reported.^{1,2} We did not attempt to document an up-regulation of HIF in the tumor, because this phenomenon is such a common signature in tumors, and a link would be difficult to assess. Furthermore, *PHD2* might have a role in an HIF-independent pathway in paragangliomas that is similar to the role played by *PHD3* in neuronal apoptosis.³ The study of conditional inactivation of *Phd2* in mice would certainly help to elucidate this issue. Finally, considering the potential tumor-suppressor function of *PHD2* suggested by our study and other observations,^{4,5} we believe that it is legitimate to recommend stringent follow-up for carriers of a *PHD2* mutation and also

to raise the issue for patients exposed to *PHD2*-inhibition therapies in the future.

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Radiation Therapy for Breast Cancer

TO THE EDITOR: In his Clinical Therapeutics article on radiation therapy for early-stage breast cancer after breast-conserving surgery, Buchholz (Jan. 1 issue)¹ states that “the breast remains tender to palpation and the skin remains hyperpigmented for 6 to 9 months after treatment but then returns to normal.” Since many readers of this informative article are not radiation oncologists, I think that it is important that this point be clarified so that normal changes that occur are not misinterpreted.

The skin of the treated breast never returns completely to normal. The treated skin is drier, often in the region of the areola and inframammary fold. Also, the degree of persistent hyperpigmentation of the skin is quite variable and is most noticeable as a rule in women with a dark complexion. There is often a variable degree of peau d'orange, in large part because of the lumpectomy and sentinel-node or axillary dissection, and it is most commonly seen in patients with large, pendulous breasts. The treated breast gen-

erally feels firmer and may have “a lift” as compared with the untreated breast.

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1. Buchholz TA. Radiation therapy for early-stage breast cancer after breast-conserving surgery. *N Engl J Med* 2009;360:63-70.

TO THE EDITOR: Buchholz points out that breast-conserving surgery followed by whole-breast irradiation for early breast cancer is the standard of care even among patients with a family history of the disease. He cites two studies published in 1998 to provide support for this inference. However, more current experimental and clinical data consistently indicate the importance of heritability in breast cancer.¹ Patients with high-penetrance heritable mutations in either the *BRCA1* or *BRCA2* gene face a 30% risk of cancer in the contralateral breast and an increased risk of ipsilateral recurrence.^{2,3}