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**THE AUTHORS REPLY:** Michiels and Hill state that validation sets 1 and 3 changed the measurement technique used to define the signature under validation, but this may be unavoidable, since we derived the initial gene signature (16 genes) using microarrays and then refined the signature to 5 genes using real-time reverse-transcriptase PCR (RT-PCR) and validated it. The 60 patients (validation 2) who were used to validate the five-gene signature constitute a completely different group from the set of 101 patients in the original cohort. In validation set 3, which involved the use of microarray data from the public domain to validate our RT-PCR signature, certain adjustments, such as using the expression level of the same gene as the reference level, were needed. We used a recursive-partitioning decision-tree model and a variable that can be used repeatedly in different nodes.

With regard to the comments of Raz and Jablons: we did not evaluate whether the five-gene signature predicts survival independently of tumor size or whether it is better than maximum tumor SUV on PET. These evaluations were not objectives of our study. Tumor stage may be more relevant than tumor size for predicting the outcome in lung cancer, and we did evaluate stage in the multivariate analysis in our study.

Dobbin remarks that there may be bias because all the data were first used to identify the informative genes and then reused when the classifier was applied to each individual sample. We identified the 16-gene signature from a training

cohort of 63 patients and then applied the linear predictor to a separate testing cohort of 62 patients without estimating the coefficients. For both cohorts, there was no reuse of data in the construction of the Kaplan–Meier curves.

With regard to the comments of Gounaris, we suggest that low-risk patients could be spared from unnecessary adjuvant treatment. We showed that the 50-month rate of overall survival among patients with a low-risk gene signature was 85% among patients with stage I or stage II disease, 65% in an independent cohort of Chinese patients, and almost 90% in an independent set of published microarray data from patients in Western countries.

Quintás-Cardama and Gibbons state that our gene signature was derived not from clinical samples but from a poorly differentiated human lung adenocarcinoma cell line, and they suggest that this approach may be flawed. The truth of the matter lies in validation of the gene signature with the use of independent cohorts of patients with NSCLC and revalidation. Cell lines can be used to derive novel invasion-suppressor genes in patients with NSCLC.<sup>1</sup> Drug-sensitivity data based on cell lines, coupled with microarray data, can be used to yield gene-expression signatures that predict the sensitivity of a tumor to chemotherapeutic drugs in patients.<sup>2</sup>

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## Childhood Progression of Hereditary Medullary Thyroid Cancer

**TO THE EDITOR:** Machens et al. (Oct. 16, 2003, issue)<sup>1</sup> confirmed that medullary thyroid carcinoma develops very early in children carrying

a germ-line mutation of the rearranged during transfection (*RET*) gene. However, an error in Figure 1 of their article may alter the message of

this important article. According to Figure 1, the risk of medullary thyroid carcinoma for a child with a codon 634 *RET* mutation is approximately 10% at 5 years of age. This finding seems to be inconsistent with the data provided by Machens et al.: that 75% of children with a codon 634 *RET* mutation (12 of 16) who underwent prophylactic thyroidectomy before the age of 5 years had medullary thyroid carcinoma.

It appears to us that the cumulative risks presented in Figure 1 have been incorrectly calculated by dividing, at each age interval, the number of children with medullary thyroid carcinoma by the total number of children (130), rather than by the number who underwent surgery at each age interval (12 divided by 130 is nearly 10%).

An international consensus established in 1999 and published in 2001 stated that all children with a codon 634 *RET* mutation should undergo thyroidectomy before 5 years of age.<sup>2</sup> Although feasible, this guideline is rarely implemented.<sup>3</sup> Correction of Figure 1 might help the medical community understand the reasons behind the guidelines.

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**THE AUTHORS REPLY:** We welcome the opportunity to illustrate the rationale behind the recommendation to perform total thyroidectomy in carriers of codon 634 *RET* mutations before the age of 5 years.<sup>1</sup> In our article on the multicenter Euro-

pean Multiple Endocrine Neoplasia (EUROMEN) study, we presented the cumulative probability of detecting medullary thyroid carcinomas before a certain age among the 130 carriers of codon 634 mutations. As noted by Chabre and colleagues, the Kaplan–Meier curve in Figure 1 cannot be construed as reflecting an age-specific malignant progression of medullary thyroid carcinoma, since this would lead to an underestimation of the risk of cancer at younger ages.

We have reanalyzed our data in order to correct the errors in our original figure (Fig. 1A), using logistic-regression analysis to enforce monotonicity of the curve<sup>2</sup> and smoothing the estimates of cancer rates by modeling the log-prevalence odds as a linear function of age. The resultant age-related malignant progression of medullary thyroid carcinoma is shown in the corrected figure (Fig. 1B). The model-based estimate of the prevalence of cancer was 52 to 66% before the age of 5 years for asymptomatic carriers of codon 634 mutations in the EUROMEN study. The corrected curve supports the need for early prophylactic thyroidectomy in asymptomatic carriers of *RET* gene mutations.

We would like to join Chabre and colleagues in their plea for widespread adoption of early thyroidectomy before the age of 5 years in carriers of high-risk *RET* mutations, including those in codon 634, to accomplish complete translation of DNA-based information from the bench to the bedside.

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