that in contrast to the correlation of mutations with responses to the \textit{EGFR} kinase inhibitors gefitinib and erlotinib, \textit{EGFR} mutations are not critical for the response of a tumor to cetuximab.

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Lack of Mutations in \textit{EGFR} in Gastroenteropancreatic Neuroendocrine Tumors

**TO THE EDITOR:** Lynch et al.\textsuperscript{3} and Paez et al.\textsuperscript{2} correlated the presence of somatic mutations in the tyrosine kinase domain of the gene that encodes the epidermal growth factor receptor (\textit{EGFR}) with responsiveness to gefitinib in non–small-cell lung carcinoma. Neuroendocrine differentiation is present in a substantial number of gastroenteropancreatic neuroendocrine tumors,\textsuperscript{3} and \textit{EGFR} expression occurs in such tumors.\textsuperscript{4}

We sought \textit{EGFR}-activating mutations in a series of rare gastroenteropancreatic neuroendocrine cancers. DNA was isolated from flash-frozen specimens of carcinoid and pancreatic endocrine tumors; \textit{EGFR} exons 18, 19, and 21 were amplified by the polymerase chain reaction with primers described by Lynch et al.\textsuperscript{1}; and amplicons were sequenced and assessed for predictive \textit{EGFR} mutations (single-nucleotide substitutions in exons 18 and 21 and in-frame deletions in exon 19). Research authorization was obtained from all the patients, and the study was approved by the institutional review board.

No mutations in the \textit{EGFR} kinase domain that were predictive of a response to gefitinib were detected in DNA from 62 human carcinoid tumors from a variety of sites, including both primary lesions (22 from the lung, 28 from the ileum, and 1 from the colon) and metastatic lesions (30 from the liver and 1 from the ovary). Most carcinoid tumors in this study were indolent; 20 matched sets, which included an ileal primary lesion and a hepatic metastatic lesion from the same patient, were examined.

As a verification of our detection procedure, DNA controls encoding \textit{EGFR} mutations L858R within exon 21, delE746-A750 within exon 19, and delL747-P753insS within exon 19 (gifts from Drs. Daphne Bell and Daniel Haber, Massachusetts General Hospital, Charlestown, Mass.) were correctly identified. We noted in one ileal carcinoid the reported germ-line synonymous coding-region single-nucleotide polymorphism C/T in \textit{EGFR} exon 21 (dbSNP:2229066; nucleotide position 2694 in GenBank accession number X00588); it was also detected in normal surrounding tissue. Similarly, no mutations in \textit{EGFR} exons 18, 19, and 21 were found in DNA from 18 primary pancreatic endocrine carcinomas. In contrast to our results, Lynch et al.\textsuperscript{1} found no mutations in \textit{EGFR} exons 19 and 21 in 40 primary pancreatic tumors (we do not know whether this group included rare pancreatic endocrine tumors) and one bronchial-carcinoid tumor-cell line.
Our results indicate that somatic activating mutations of the EGFR kinase domain that are predictive of responsiveness to gefitinib are uncommon in gastroenteropancreatic neuroendocrine cancers, pancreatic endocrine carcinomas, and carcinoid tumors (primary as well as metastatic lesions).

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