Mutations in TP53 are common in non–small cell lung cancer. Apart from the loss of tumor-suppressor functions, TP53 mutations may result in gain of function favoring cellular proliferation, inhibition of apoptosis, and genomic instability. Some TP53 mutations are more likely to affect the course of the disease than others. Clin Cancer Res; 20(17); 4419–21. ©2014 AACR.
Conformational changes can interfere with the recognition of DNA binding elements that are normally recognized by wild-type TP53 and uncover hitherto hidden interfaces in these DNA binding domains. Another practical way to categorize TP53 mutations is as disruptive or non-disruptive based on the location of the mutation and the predicted amino acid alterations (12). Mutations resulting in the substitution of amino acids belonging to a different polarity and charge in the L2 and L3 regions of the DNA binding domains, or stop codon, are classified as disruptive. All other mutations are categorized as nondisruptive. Importantly, these mutations have already been characterized for their cellular effects using human cell systems and mouse models. Many nondisruptive variants are GOF mutations that mediate oncogenesis through mechanisms already described.

Molina-Vila and colleagues examined retrospectively the impact of TP53 mutations in 318 patients with stage IIIB–IV NSCLC, including 125 patients with EGFR wild-type mutations (1). In the group of patients with EGFR wild-type mutations...
NSCLC, the median overall survival was significantly lower in those with nondisruptive TP53 mutation than those whose tumor cells had either wild-type TP53 or with a disruptive TP53 mutation (8.5 months vs. 15.6 months respectively, \( P = 0.003 \)). This difference was seen even in the EGFR-mutant group (17.8 months vs. 28.4 months, \( P = 0.04 \)), underscoring the significant effect of nondisruptive TP53 mutations independent of EGFR status. These findings were confirmed in a small independent cohort of patients with EGFR-mutant NSCLC. However, these findings are directly in conflict with the results from Poeta and colleagues (12), who reported worse outcomes in early-stage head and neck cancers harboring disruptive TP53 mutants. It is possible that specific TP53 mutants may exert unique and seemingly conflicting effects based on the tissue of origin and concomitant genomic alterations. Clearly, more studies need to be done to validate or refute these observations.

Fortunately, ongoing studies by TCGA and other large-scale genomic studies will provide a large body of information on TP53 mutation status from several thousand patients with NSCLC (Fig. 1). Integration of transcriptomic and proteomic studies will enable us to tease out the downstream effects of the various classes of TP53 mutations in the coming years. Parsing these data carefully using well-curated clinical specimens and follow-up functional studies will shed more light on the in vivo effects of various mutations involving TP53. Disappointingly, therapeutic strategies directed toward TP53 alterations have largely failed. Many such strategies focused on the reactivation of TP53 in cancer cells, with the hope of restoring its tumor-suppressor properties. Characterizing the downstream pathways activated by TP53 GOF variants is a critical first step before developing therapies aimed at functionally reestablishing the master regulator that goes awry in so many cancers.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

Conception and design: R. Govindan

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Govindan

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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Govindan

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TP53 Mutations and Lung Cancer: Not All Mutations Are Created Equal

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