**Introduction**

Gastric cancer is the second leading cause of cancer deaths of global death and the fourth most common cancer worldwide. The prognosis of patients diagnosed with gastric cancer continues to be dismal, despite improving surgical and adjuvant treatment approaches, with a 5-year overall survival less than 25% [1]. The high disease incidence and poor outcomes continue to make gastric cancer a topic of active clinical and basic scientific research. Despite these efforts, relatively little is known about the molecular changes that contribute to the development of this deadly disease and how they may influence outcomes and therapeutic results.

Gastric cancer is a heterogeneous disorder that can be divided into at least the following two main histologic types on the basis of the Lauren classification: intestinal and diffuse types.

Gastric cancer can be considered a multifactorial disease because many inherited and environmental factors play a role in its carcinogenesis, including the genetic background of the host, infectious agents such as *Helicobacter pylori*, and dietary habits. These two types have distinct morphologic, clinical, and epidemiologic features and may also represent a different molecular mechanism of tumor development and progression [2].

The identification of germline E-cadherin (CDH1) mutations in families with hereditary diffuse gastric cancer provided early insight into the initial changes that promote gastric tumorigenesis and...
established CDH1 as a bona fide tumor suppressor. Subsequent studies indicated that, although germline CDH1 mutations are common in hereditary gastric cancer of the diffuse, but not intestinal, type, somatic mutations in CDH1 are frequently identified in sporadic gastric cancer of both major histologic subtypes. In addition, somatic epigenetic alterations, such as CDH1 promoter hypermethylation, are present in diffuse- and intestinal-type tumors and result in gene silencing. This epigenetic silencing of CDH1 gene expression represents the “second hit” in approximately 50% of hereditary diffuse gastric cancers, whereas the prevalence of CDH1 promoter hypermethylation in sporadic gastric cancers ranges in estimates from 11% to 46% depending on the histologic subtype.

Relatively small sample sizes and a focus on hereditary cancers or a single histologic subtype have hampered previous studies that evaluated the prevalence of CDH1 somatic mutations in gastric cancer overall.

The current study by Corso et al. evaluated a large set of familial and sporadic gastric cancers to provide a more comprehensive analysis of the prevalence of CDH1 somatic mutations and their correlation with patient survival. The authors analyzed 246 patients with sporadic (n = 174) or familial (n = 72) gastric cancer for CDH1 structural changes (either mutation or loss of heterozygosity) or epigenetic alterations (CDH1 promoter hypermethylation). The results indicated that, overall, 31% of gastric cancers carried CDH1 alterations, two thirds of which were epigenetic alterations and one third of which were structural alterations. Patients with CDH1 structural alterations displayed a poorer overall survival than in patients with either no changes or epigenetic changes only.

In addition, the authors report that CDH1 alterations (both structural and epigenetic) were found in 27.5% of intestinal-type and 38.4% of diffuse-type gastric cancers. Although these alterations were not associated with a worse overall survival in patients with diffuse-type tumors, there was a strong association between CDH1 structural alterations and poorer overall survival in patients with intestinal-type tumors.

The major finding by Corso et al. is that nearly one third of gastric cancers harbor somatic CDH1 alterations and those with structural alterations carry a poorer prognosis. This raises the question of whether somatic CDH1 alterations should influence the clinical management of gastric cancer. Although the findings in this study significantly clarify the extent of somatic CDH1 alterations in gastric cancer, there continues to be insufficient evidence to warrant regular CDH1-alteration analysis as a standard prognostic indicator or for predictive use in therapeutic decision making. However, the incorporation of this and other molecular features to more specifically characterize gastric cancers should certainly be part of the design of prospective studies of surgical and adjuvant therapy for this disease.

The role of epigenetic changes and tumor-suppressor silencing through promoter hypermethylation in human cancers has raised the specter of the use of demethylating agents such as 5-azacytidine as a therapeutic intervention. Large-scale changes in DNA methylation have been noted in the gastric cancer genome, and the CpG island methylator phenotype may predict a poor outcome independent from the tumor stage. A large number of genes that are suppressed by hypermethylation have been reported in gastric cancer in addition to CDH1, including the DNA mismatch repair genes, CDKN2A (p16), and MGMT (O6-methylguanine DNA methyltransferase). Whether therapeutic demethylation of some or all of these genes in gastric cancer may lead to tumor responses has yet to be tested. The use of demethylating agents has also been considered a potential chemoprevention strategy for carriers of the germline CDH1 mutation to slow or reverse the epigenetic second hit that inactivates CDH1 expression.

Although such an epigenetically targeted approach awaits additional investigation in gastric cancer, there is mounting evidence that somatic alterations, including copy-number variations in key oncogenes, such as amplifications of HER2, FGFR2, and MET represent viable treatment targets for which therapeutics are already approved or currently under investigation.

Individual molecular profiling of gastric cancers at a whole-genome level have revealed several known (e.g., p53, PTEN, and PIK3CA) as well as previously unreported (ARID1A) somatic gene mutations and pathway alterations. Of more immediate
potential application, somatic copy-number aberrations have been found to be common in upper-GI cancers; 28% of gastric cancers have been shown to harbor amplifications in targetable membrane tyrosine kinases.

The HER2 oncogene has been found to be amplified in from approximately 12% to greater than 20% of gastric cancers, and a phase III trial that investigated trastuzumab treatment of HER2-positive gastric cancers demonstrated an increased overall survival and response rate. Additional amplified genes that are currently being explored as therapeutic targets in the clinic include FGFR2, EGFR, and MET. Small molecules and therapeutic monoclonal antibodies are in development for each of these targets, and their role in gastric cancer as single agents and in combination with chemotherapy is being explored in ongoing phase I and II trials. Early results suggested that amplifications of each of these potential targets occur in from approximately 5% to 15% of gastric cancers. However, whether they are mutually exclusive or whether various combinations of these oncogenic targets will occur in individual tumors remains unknown. Furthermore, significant genetic heterogeneity has been shown to occur within and between primary cancers and individual metastatic sites.

This heterogeneity is clearly the case for gastric cancers as well and will prove challenging for rationally designed targeted-therapy approaches. Nevertheless, initial studies, such as the one by Corso et al., in the current issue of Journal of Clinical Oncology, and others are defining the genetic and epigenetic landscape of gastric cancers. These studies suggest, as has been appreciated in breast cancer for sometime, that multiple genetic and molecular subtypes of gastric cancer exist beyond those defined histologically, and the genomic profiling of individual tumors may present unique treatment options for patients. As genomic analyses become an increasingly available option for the evaluation and identification of treatment targets in the tumor of an individual, clinical oncologists will have more therapeutic options at their disposal but will also be required to understand the genetics of the diseases of their patients.

Conclusion:
The goal of personalized cancer medicine is to understand the relevant genetic factors that underlie the particular tumor of an individual and tailor therapy to that individual.

REFERENCES