risk? Perhaps, it is time to abandon this one-size-fits-all approach and adjust surveillance practices to reflect the growing consensus of substantially reduced risk estimates for nondysplastic Barrett's in recent reports.

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Expanding the Lauren Classification: A New Gastric Cancer Subtype?

See "Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil," by Lei Z, Tan IB, Das K, et al, on page 554.

Adenocarcinoma of the stomach remains a major public health issue. Although the incidence of this cancer in the United States has been falling, with only 21,600 new cases expected in 2013,[1] the prognosis for patients remains grim. Despite improvements in treatment approaches, 5-year survival remains at <30%.[1] In addition to the typically advanced stage of diagnosis for most gastric adenocarcinomas, these dismal survival statistics reflect the lack of effective treatment options. Identifying specific signaling pathways in individual patients might improve treatment outcomes, but only limited data are available. In this issue of GASTROENTEROLOGY, Lei et al[2] describe an approach to overcoming this obstacle. Their results identify 3 molecular signatures of gastric adenocarcinoma (Table 1). Patient survival data indicate that one of these subtypes may best be treated using 5-fluorouracil. In vitro data also suggest that another subtype may be particularly sensitive to phosphatidyl-inositol-3-kinase inhibitors.

This study builds on previous mRNA analyses of gastric cancers by this group and others.[3–10] By combining 192 previously reported[9] and 56 new microarray expression profiles, Lei et al[2] created a database describing 248 Singaporean primary gastric cancers. These were broken into 3 unique groups using hierarchical clustering with iterative

Table 1. Gastric Adenocarcinoma Classifications

	Lauren (1965)		Lei et al. (2013)		
	Diffuse	Intestinal type	Mesenchymal	Proliferative	Metabolic
Intestinal type morphology	0%[a]	100%[a]	30%[a] (7%)[b]	74%[a] (71%)[b]	54%[a] (84%)[b]
Diffuse morphology	100%[a]	0%[a]	59%[a] (93%)[b]	17%[a] (29%)[b]	41%[a] (16%)[b]
Intestinal metaplasia	55%	91%			
Chronic gastritis	45%	88%			
Copy number alteration			Low	High	
Amplified genes				CCNE1, MYC, ERBB2, KRAS	
Aberrant methylation			Hypermethylation	Hypomethylation	
TP53 mutations			Low	High	Low

[a]Classification based on criteria of Lauren (1965).[11]
[b]Classification based on criteria of Tan et al. (2011).[7]

feature selection. The 201 gastric cancers that best represented the 3 groups were used to develop classification algorithms. The algorithms were then validated using a separate set of 70 Australian primary gastric cancers. The data show that at least for gastric cancers arising in Singapore and Australia, subclassification into the 3 groups is reproducible.

To better understand the biological significance of the distinct groups, Lei et al[2] examined the differentially expressed genes. The clusters were designated as mesenchymal, to reflect expression of genes in the epithelial-mesenchymal transition pathway; proliferative, because growth promoting oncogenic pathways were activated; and metabolic, owing to expression of genes associated with metabolic pathways.

Further analyses of each group showed that mesenchymal tumors lost expression of E-cadherin, the epithelial cadherin isoform. Consistent with the frequent loss of E-cadherin expression in signet ring cell gastric cancers, nearly 60% of mesenchymal tumors were classified as Lauren's diffuse type (Figure 1*A*), and 70% had at least some features of diffuse gastric cancer.[11] Further, consistent with reports that diffuse gastric cancers tend to be hypermethylated,[12] mesenchymal tumors displayed genomic hypermethylation. Transforming growth factor-β, vascular endothelial growth factor, nuclear factor-κB, mammalian target of rapamycin, sonic hedgehog, and cancer stem cell pathways were also activated in mesenchymal gastric cancers. In contrast, p53 mutations and DNA copy number variations were limited.

In contrast with mesenchymal gastric adenocarcinomas, nearly 75% of proliferative tumors were Lauren's intestinal type (Figure 1*B*). These tumors tended to have activation of E2F, MYC, and RAS pathways and mutations of *CCNE1*, *MYC*, *ERBB2*, and *KRAS*. Proliferative cancers were hypomethylated and often harbored p53 mutations. These characteristics suggest that the proliferative cluster overlaps with Lauren's intestinal type and that this group includes tumors responsive to therapies targeting epithelial growth factor receptor (EGFR), ERBB2, and growth factor or stem cell pathways.

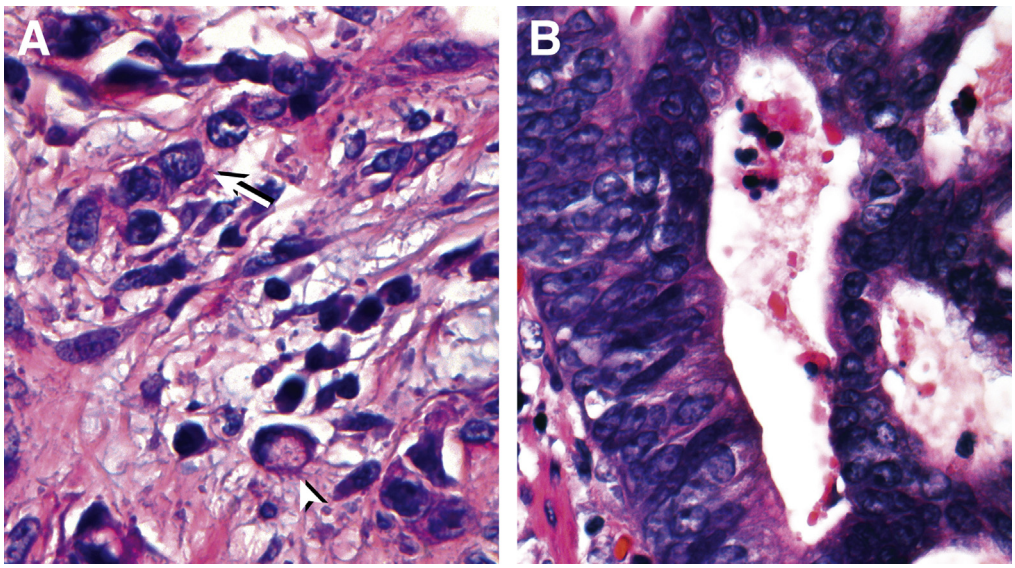

Figure 1. Classic Lauren gastric cancer subtypes. (*A*) Diffuse gastric cancers are most often composed of signet ring cells and infiltrate as individual cells (*arrowhead*) or single-file lines (*arrow*). Mucin is deposited within the tumor stroma. (*B*) Intestinal-type gastric cancers are composed of tall columnar cells arranged in glands. Mucin and necrotic debris is deposited within the gland lumens.

The real surprise of this paper is the presence of a third gastric adenocarcinoma cluster. Why did this study identify 3 groups when previous molecular analyses, including those by this same group using many of the same gastric cancer specimens, found only 2? One possibility is the hierarchical clustering analysis employed here. Although powerful, this approach requires the user to predefine the number of clusters in the data set. Lei et al[2] determined the correct number of clusters empirically. Increasing the cluster number from 2 to 3 improved the statistical accuracy of subclassification, whereas further cluster number increases provided only minimal benefit. This led Lei et al[2] to postulate that 3 subtypes of gastric cancer were present in the set. The differences between the 3 groups identified support this hypothesis.

The mesenchymal and proliferative subtypes largely coincide with Lauren's diffuse and intestinal subtypes. So what is the third type of gastric cancer? Histologically, these tumors are nearly evenly split between diffuse and intestinal types. There are no characteristic gene amplifications, and p53 mutations are rare. It is therefore understandable that the so-called metabolic type tumors were lost within the diversity of diffuse and intestinal type tumors in previous analyses. However, it is notable that the metabolic tumor group includes features of spasmolytic polypeptide-expressing metaplasia.[8,13]

Armed with this new information, Lei et al classified gastric cancer cell lines as mesenchymal, proliferative, or metabolic and tested their in vitro sensitivity to chemotherapeutic agents. Remarkably, metabolic tumors were highly sensitive to 5-fluorouracil. This seems to also be true in vivo, because 5-fluorouracil treatment was associated with 100% 5-year survival among Singaporean patients with metabolic type gastric cancers. Cancer-specific, disease-free survival was also improved and, after adjusting for TNM stage, overall survival was also enhanced by 5-fluorouracil treatment in Australian metabolic tumors. Lei et al also found that mesenchymal-type gastric cancer cell lines were more sensitive to phosphatidyl-inositol-3-kinase inhibitors in vitro, although in vivo patient data are not available.

While these data are striking, one might question the dependence on retrospective review of pathology reports, which are recognized to be unreliable owing to variation in classification criteria over time. How could review of the actual histopathology have added to the hierarchical clustering analysis? Although long forgotten, it is worth noting that Lauren's landmark study was not simply a description of intestinal-type and diffuse gastric adenocarcinomas. This 1965 work was a detailed study that analyzed morphologic data in a manner similar to that in which molecular data are now used. Multiple tumor characteristics were collected and clusters were combined when they were found to overlap significantly. Ultimately, Lauren was left with 2 primary groups: Intestinal type and diffuse. In addition to the distinctive architecture and cytology, these subtypes also differed in that intestinal type cancers presented a decade later than diffuse adenocarcinomas. Lauren also found that intestinal-type tumors were associated with chronic gastritis and intestinal metaplasia in 90% of cases, whereas only half of diffuse cancers had these features. Thus, intestinal-type, or proliferative, cancers likely develop as a result of chronic gastritis and intestinal metaplasia, whereas diffuse, or mesenchymal, adenocarcinomas do not. The new molecular data further suggest that the metabolic subtype defined by Lei et al may originate within spasmolytic polypeptide-expressing metaplasia.[13]

Inclusion of classic histologic data, as well as degree of differentiation, mitotic rate, and presence of spasmolytic polypeptide-expressing metaplasia, may have greatly enriched Lei's analysis and minimized the redundancy apparent in the tendency of mesenchymal gastric cancers to be diffuse and of proliferative tumors to be intestinal type. Adding histopathology to the cluster analysis might have also provided tools for development of a simpler means to identify 5-fluorouracil–sensitive tumors. This approach has been successful in identifying subgroups of other tumors. For example, histologic separation of desmoplastic small cell tumors from a larger group of small, blue, round cell tumors made it possible to recognize that these lesions had a characteristic chromosomal translocation resulting in a EWS–WT1 gene fusion.[14,15] Detection of this fusion protein is now part of the standard diagnostic workup of small, blue, round cell tumors and is used to identify desmoplastic small cell tumors within that group. Similarly, histology and assay of a select set of genes and proteins might provide an effective means to subclassify gastric adenocarcinoma. The latter might include simple immunohistochemistry or molecular analyses of p53, MYC, EGFR, ERBB2/Her2, K-RAS, Ki67, mucin genes, stem cell markers, thymidylate synthase, and dihydropyrimidine dehydrogenase (low expression of thymidylate synthase and dihydropyrimidine dehydrogenase are associated with favorable 5-fluorouracil responses in colorectal cancer[16]). Notably, recent reports have used either a simple 6-gene panel or the combination of well-differentiated intestinal-type and microsatellite instability as markers of 5-fluorouracil–sensitive gastric adenocarcinomas.[3,17]

Overall, the study by Lei et al[2] and similar reports[3–10,17] represent new hope for personalized therapy of gastric adenocarcinoma. Finding ways to apply this information to identify tumor subsets and develop molecularly tailored, individualized therapies will require creative thinking in this era of evidence-based, cost-effective medicine.

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Do Therapeutic Bile Acids Hit the Sweet Spot of Glucose Metabolism in NAFLD?

See "Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease, by Mudaliar S, Henry RR, Sanyal AJ, et al, on page 574.

It has been known for almost 15 years that bile acids have broad and powerful hormonal properties as gene regulators that parallel their previously well-established physiologic roles in choleresis and digestion.[1–4] These amphipathic cholesterol-derived molecules are perfectly poised to act in the disposition of food as well as participate in energy homeostasis owing to their physical properties as well as locations deeply enmeshed in the luminal milieu, enterocyte, and hepatocyte interior as they course through their roles in the enterohepatic circulation.[5–9] It makes sense to think of these molecules as, arguably, the perfect sensors, sentries, and deliverymen of molecular information and nutrients to these central components of health, growth, and interactions with the ingested world. Even a cursory look at bile acid structure and the ever-expanding identification of intracellular targets now place this class of molecules squarely as effectors, integrators, and key regulators of metabolism.

In essence, given the multitudinous roles played by bile acids, these molecules can be colloquially described as steroids "on steroids"—meaning that as hormones they have transcriptional, signaling, and luminal actions—arguably the most far-reaching signaling effector molecules in the body. In particular, as transcriptional regulators, bile acids