high-risk groups may be considered for investigational medical therapies, and patients in the high, very high, and even pre-terminal risk groups may, in addition, be candidates for studies using bioartificial liver support devices. The costs associated with care of patients in specific risk groups can also be studied and results may be used in making treatment decisions. Future studies should incorporate biomarkers, as well as genetic markers to improve the accuracy of the current combined MELD and Lille score model.

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Conflicts of interest
The authors disclose no conflicts.

Funding
National Institutes of Health (NIH) U01 AA 21788.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.06.020

New Molecular Tools to Investigate the Development and Functions of Interstitial Cells of Cajal in the GI Tract

See "LRIG1 regulates ontogeny of smooth muscle–derived subsets of interstitial cells of cajal in mice," by Kondo J, Powell AE, Wang Y, et al on page 407.

Major motility patterns of gastrointestinal (GI) organs were thought traditionally to be determined mainly by myogenic and neurogenic mechanisms. More recently interstitial cells have been recognized as contributing important regulatory functions in GI motor

activity.[1] At least 2 types of resident interstitial cells (interstitial cells of Cajal [ICC] and PDGFRα^+ cells) lie in close proximity to the terminals of enteric motor neurons. Together with smooth muscle cells, ICC and PDGFRα^+ cells form an electrical syncytium (SIP syncytium) and integrate inputs from enteric motor neurons. ICC are also the pacemakers that generate electrical slow waves in the GI tract.

A review published in *Gastroenterology* 20 years ago summarized some of the important functions of ICC in GI motility that had been gleaned from studies of mutant mice.[2] W/W^V mice have mutations in *Kit*, and they fail to develop certain classes of ICC and display distinct phenotypes. For example, in the small intestine the ICC of the myenteric region failed to develop (ICC-MY), but the ICC intermingled with muscle fibers in the deep muscular plexus (ICC-DMP) of the small intestine developed normally. Loss of ICC-MY left the small intestine void of electrical slow waves and slowed intestinal transit.[3,4] In contrast, ICC-MY and slow waves seemed to develop normally in the stomach. However, gastric intramuscular ICC (ICC-IM) were largely absent, and nitrergic and cholinergic enteric motor neurotransmission were compromised.[5] These findings led to the idea of a "division of labor" between the different classes of ICC in the gut.[2] Unfortunately, the tools available to investigate the roles of specific populations of ICC have been minimal. An article published in this issue of *Gastroenterology* from the Coffey laboratory[6] introduced a powerful new molecular regulator of the development of ICC-DMP and ICC along the submucosal surface of the circular muscle layer in the colon (ICC-SMP). These authors found that Leucine-rich repeats and immunoglobulin-like domains protein 1 (Lrig1) is expressed preferentially in ICC-DMP versus ICC-MY in the small intestine and in ICC-SMP in the colon. An earlier gene array screen of the ICC transcriptome from small intestinal ICC found that *Lrig1* is highly expressed in ICC-DMP.[7] However, *Lrig1* was also expressed, albeit at lower levels, in ICC-MY (ie, expression of *Lrig1* in ICC-DMP was an average of 4-fold greater than in ICC-MY). The recent study by Kondo et al[6] demonstrated the importance of Lrig1 expression in ICC-DMP and ICC-SMP by showing that it is a key determinant in the development of these cells (Figure 1).

Development of ICC has been investigated, but many questions, such as the source of ICC-DMP and ICC-SMP and why these cells develop much later than ICC-MY, were unanswered by previous studies. The development of ICC-DMP and ICC-MY may be regulated differentially, because these cells display different dependencies on c-Kit.[3,4,8] Use of neutralizing antibodies suggested that c-Kit signaling is ultimately important for the development of all ICC.[9] However, other factors may be able to compensate for c-Kit when this pathway is compromised, as in W/W^V mice, or be obligatory in addition to c-Kit signaling. Kondo et al[6] confirmed that ICC-DMP arise in the small intestine within the first 10 days after birth, and fate mapping indicated that these cells emerge from circular smooth muscle cells (CSMC). Expression of c-Kit was resolved only in ICC-MY at birth, and at this point in time, CSMC expressed Lrig1 (Figure 1). With time, Lrig1 decreased in CSMC in the outer portion of the circular muscle layer, but was retained in cells near submucosal surface. Eventually c-Kit developed in Lrig1$^+$ cells as these cells matured into ICC-DMP. A similar sequence of events occurs in the development of ICC-SMP in the colon. ICC-DMP failed to develop in mice null for *Lrig1*. How Lrig1 is fundamental for the development of specific classes of ICC is yet to be determined, but the discovery of this molecular switch may provide new opportunities for investigating the function of specific classes of ICC in the small intestine and colon.

ICC are lost in a variety of motility disorders and previous pathologic reports have largely been confined to evaluations of c-KIT and recently to ANO1 expression.[10] Because of the discrete distribution of ICC-MY and ICC-DMP in mice (they appear in 2 well-defined lines of cells in cross sections), it is relatively easy to identify loss of 1 layer or the other, as demonstrated in the study by Kondo et al.[6] However, clear identification of ICC-DMP in the human small intestine is confused by a more diffuse distribution of c-Kit$^+$ cells (including intramuscular ICC).[1] Thus, development of new biomarkers and immunologic tools will be needed to more clearly identify the types of ICC loss occurring in motor pathologies.

The ability to raise mice to adulthood with reduced ICC-DMP and ICC-SMP provides opportunities for more direct tests of the role of these cells in normal and abnormal motility. Previous studies noted defects in enteric motor neurotransmission in mice treated from birth with neutralizing antibodies,[9] and post-junctional neural responses developed in phase with the development of ICC-DMP and were reduced when ICC-DMP development was impeded.[11] A recent study suggested that Ca^{2+} signaling in ICC-DMP is responsible for the motor pattern of segmentation.[12] The colon has 2 pacemaker regions, and ICC-SMP were found to be responsible for generation of slow wave potentials, in contrast with the stomach and small intestine where ICC-MY have this function.[13] Therefore, loss of ICC-SMP would be predicted to have significant effects on electrophysiologic patterns in colonic muscles. Animals with specific lesions in ICC-DMP and ICC-SMP would be very useful for direct tests of the hypotheses proposed from observations on intact tissues. The new experimental tools developed by Kondo et al[6] may allow new understanding of how ICC-DMP and ICC-SMP contribute to the integrated behaviors of the SIP syncytium.

Kondo et al[6] tested the impact of deactivating *Lrig1* on motility of the small intestine by measuring intestinal transit (using the geometric center technique). *Lrig1*$^{+/-}$ mice showed essentially normal transit, but transit was retarded in *Lrig1*$^{-/-}$ mice. No differences in gastric emptying or in the length of the small intestine were observed in mice null for *Lrig1*. A link between the transit defect and the developmental failure of ICC-DMP was suggested but not yet proven. More mechanistic studies on the specific physiologic