screening and surveillance strategy. Although questions remain to be answered, this study shows the potential of next generation sequencing with a multigene panel for the evaluation of hereditary cancer syndromes.

VEROUSHKA BALLESTER
LISA BOARDMAN
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

References

1. Yurgelun MB, Allen B, Kaldate RR, et al. Identification of a variety of mutations in cancer predisposition genes in patients with suspected lynch syndrome. Gastroenterology 2015;149:604–613.
2. Stoffel EM, Kastrinos F. Familial colorectal cancer, beyond Lynch syndrome. Clin Gastroenterol Hepatol 2014;12:1059–1068.
3. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening of Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783–5788.
4. Domcheck SM, Bradbury A, Garber JE, et al. Multiplex genetic testing for cancer susceptibility: out on the high wire without a net? J Clin Oncol 2013;31:1267–1270.
5. Kievit W, de Bruin JH, Adang EM, et al. Current clinical selection strategies for identification of hereditary non-polyposis colorectal cancer families are inadequate: a meta-analysis. Clin Genet 2004;65:308–316.
6. Balmana J, Balaguer F, Castellvi-Bel S, et al. Comparison of predictive models, clinical criteria and molecular tumor screening for the identification of patients with Lynch syndrome in a population-based cohort of colorectal cancer patients. J Med Genet 2008;45:557–563.
7. Giardello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2014;109:1159–1179.
8. Labadaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69–79.
9. Farrugia DJ, Argal MK, Pankratz VS, et al. Functional assays for classification of BRCA2 variants of uncertain significance. Cancer Res 2008;68:3523–3531.
10. Cragun D, Radford C, Dolinski JS, et al. Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a US laboratory. Clin Genet 2014;86:510–520.
11. Peterlongo P, Nafa K, Lerman GS, et al. MSH6 germline mutations are rare in colorectal cancer families. Int J Cancer 2003;107:571–579.
12. Plon SE, Cooper HP, Parks B, et al. Genetic testing and cancer risk management recommendations by physicians for at-risk relatives. Genet Med 2011;13:148–154.
13. Gallego CJ, Shirts BH, Bennette CS, et al. Next-generation sequencing panels for the diagnosis of colorectal cancer and polyposis syndromes: a cost-effectiveness analysis. J Clin Oncol 2015;33:2084–2091.

Reprint requests
Address requests for reprints to: Lisa Boardman, MD, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, Minnesota 55905. e-mail: Boardman.lisa@mayo.edu.

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Trials and Tribulations: The Prevention of Variceal Rebleeding

See "Prevention of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents vs hemodynamically controlled medical therapy," by Sauerbruch T, Mengel M, Dollinger M, et al, on page 660.

The last 25 years of portal hypertension clinical research has directly resulted in a reduction in variceal bleeding mortality from 50% to 20%. This research has included introduction of new techniques, technological refinements, and application of old treatments/concepts in new combinations. It is important to know how we got to where we are, to know where we should go next, so that the constant refinement of the patient journey continues. The paper by Sauerbruch et al[1] in this issue of *Gastroenterology* is another step on that journey.

Critical milestones include the discovery that β-blockers lower portal pressure in a proportion of patients with cirrhosis[2] (akin to identifying a drug that lowers systemic blood pressure) and that measurement of the hepatic venous pressure gradient (HVPG) is a good indicator of portal pressure (the "blood pressure cuff" of the splanchnic circulation) Threshold values for clinical events have been determined (Table 1) providing targets to aim for.[3–5] As a consequence of this early clinical research, β-blockers became the drug of choice in primary prophylaxis (prevention of the first bleed) and were superior to needle sclerotherapy—an endoscopic technique blighted by serious side effects of ulceration, stricturing and sepsis—in secondary prophylaxis (prevention of subsequent bleeding.) The introduction of banding then changed the landscape for the endoscopists in that it was easier, safer, and found to be superior to needle sclerotherapy.[6] Therefore, it was logical that banding needed to be compared with drug therapy

Table 1. HVPG Threshold Values for Clinical Events

HVPG value	Clinical Event
>10 mm Hg	Risk of developing portal hypertension related complications (variceal bleeding, ascites, hepatic encephalopathy)
>12 mm Hg	Increased risk of variceal bleeding
>16 mm Hg	Increased mortality risk
>20 mm Hg	Increased risk of treatment failure and mortality during variceal bleeding
>20% HVPG reduction or HVPG <12 mm Hg on treatment	Decrease in the risk of variceal bleeding, development of ascites, spontaneous bacterial peritonitis or death

HVPG, hepatic venous pressure gradient.

(either β-blockers alone or in combination with nitrate). Various metaanalyses showed that although banding was associated with a slightly decreased bleeding rate, there was no difference in mortality.[7] Very few trials used HVPG measurement to establish whether the drug arm was actually doing what it set out to do (ie, lowering portal pressure) and, as a consequence, dose adjustments were somewhat empirical and based on patient tolerance as much as anything (and therefore not reflecting the practice of systemic blood pressure management). At around the same time, the transjugular intrahepatic portosystemic shunt (TIPS) arrived on the scene. The concept was developed in animals in 1979,[8] and then applied to humans in 1989 with the critical advance being the maintenance of the intrahepatic channel with a stent.[9] As with many new techniques, it was initially used on the sickest patients as "rescue" or "salvage" therapy (ie, patients who had continued to bleed despite drug and endoscopic therapy, and who often had more advanced liver disease). TIPS reintroduced the concept of shunt therapy, which had largely fallen out of favor because of the high morbidity associated with surgical shunts.[10] With its enthusiastic adoption, it became clear that trials comparing radiologic shunting with endoscopic and/or drug therapy would be a logical avenue of exploration. Although metaanalysis showed a decreased incidence of rebleeding, the incidence of encephalopathy was significantly increased in the TIPS arm, and there was no survival benefit.[11] The TIPS group was troubled by a high stenosis rate, which was $\leq$50% at 1 year depending on whether this was measured directly by pressure, indirectly by Doppler ultrasonography, or clinically by events such as ascites or rebleeding. This had a major impact not just on the patient outcome but also financially—the bare metal stents were "high maintenance." Thus the introduction of polytetrafluoroethylene (PTFE)-covered stents with their significantly lesser stenosis rate[12] and perhaps surprisingly reduced encephalopathy rates was the next "game changer," and these stents have been adopted widely.

Two further landmark trials identified that early radiologic shunting improved survival in high-risk patients with acute variceal bleeding.[13,14] This approach, born from surgical experience,[15] identified patients with acute variceal bleeding who had indices for poor outcome (either high HVPG or clinical/laboratory criteria) and showed that preemptive TIPS improved survival. Prompt shunting decreased rebleeding and had a beneficial effect on survival. As will be discussed, the timing of the intervention is important.

This brings us to the current period, and at the most recent Baveno VI meeting held in April 2015 (aimed at understanding the pathophysiology of portal hypertension, and developing treatments and strategies for managing variceal bleeding), one of the gaps highlighted was defining the secondary prophylaxis of choice in patients who have had a variceal bleed but did not undergo urgent TIPS. There was general agreement that the ideal trial using drug therapy should attempt to determine whether the drug is having an hemodynamic effect by measuring HVPG, or should use both banding and drug therapy in combination (because that is now the common practice worldwide.) It was also clear that the technical revolution of PTFE-lined stents meant that elective TIPS in secondary prophylaxis should now be reexamined; and encephalopathy (overt and subclinical) should be critically evaluated, as the latter particularly is underestimated.

In this issue of *Gastroenterology*, the German Study Group for the Prophylaxis of Variceal Rebleeding attempt to answer some of these questions. Principally, is a covered TIPs (group A) better secondary prophylaxis than medical therapy/banding (group B)? Patients with advanced liver disease were excluded, because their encephalopathy rates are very high when shunted. The authors used 8-mm PTFE-coated stents, presumably to further reduce the risk of encephalopathy. Patients in group B underwent baseline HVPG, and were then started on propranolol 40 mg twice daily; the dose was up-titrated to achieve a 25% decrease in heart rate or maximum tolerated dose—at which point 20 mg twice daily isosorbide-5-mononitrate was added. At 2 weeks the HVPG was repeated, and those deemed to be nonresponders (presumably, but not stated in the manuscript, reflecting an HVPG reduction of <20%) were switched to banding. Switching to and not adding band ligation may have been a penalty for this arm of the study. Indeed, nonselective β-blockers have demonstrated beneficial effects beyond their capacity to decrease portal pressure[16] and it usually recommended in nonresponders to add and not switch to esophageal band ligation.

The intention-to-treat/per-protocol numbers (92/88 in group A and 95/81 group B) seem to provide adequate power. However, 187 patients were randomized from a total of 836 (22%), and although the authors have provided a breakdown of the excluded patients, this high number reflects a confusing randomization process that critically allowed patients to be randomized over a wide range of times after the index bleed. Although this may be a reflection of real life where patients can be referred quite late for treatment, it may introduce a selection bias. We do not know which treatment was applied to these patients, if any, from the index bleed until the application of the allocated treatment and also the number of patients that rebled or