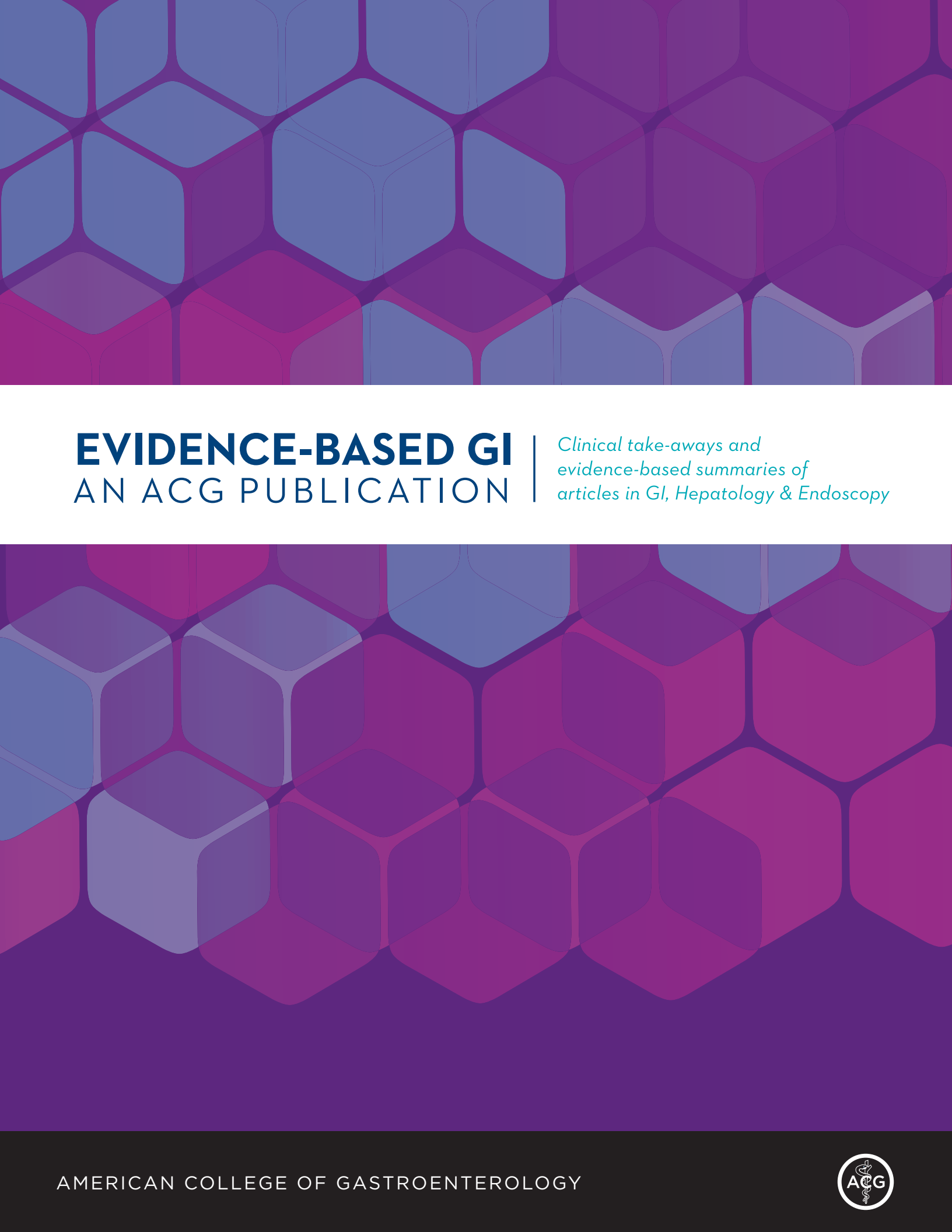




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ESD vs TAMIS for Early Rectal Neoplasms



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This summary reviews de Frutos Rosa D, Alonso Sebastián I, Barquero Declara D, et al. A randomized trial of endoscopic submucosal dissection vs transanal minimally invasive surgery in early rectal neoplasms: DSETAMIS-2018 Study. *Gastroenterology*. 2026;170(1):161-173.

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Keywords: Early rectal neoplasms, endoscopic mucosal resection, transanal minimally invasive surgery, randomized controlled trial

STRUCTURED ABSTRACT

Question: Is endoscopic submucosal dissection (ESD) noninferior to transanal minimally invasive surgery (TAMIS) for preventing local recurrence after local resection of early rectal neoplasms?

Design: Multicenter, open-label, parallel-group, noninferiority randomized controlled trial with 1:1 allocation. Patients were assigned through simple unrestricted randomization using a computer-generated sequence, with allocation concealment through the REDCap randomization module. Blinding of participants and procedural investigators was not feasible because of the inherent differences between the 2 treatment strategies and their associated care protocols.

Setting: Three tertiary academic hospitals in Spain enrolled participants from April 2019 through December 2023.

Patients: Adults with nonpedunculated sessile, laterally spreading rectal lesions

>20 mm in diameter, located between 3 and 14 cm from the external anal margin, with circumferential involvement $\leq 50\%$, and no clinical suspicion of deep submucosal invasion. Seventy-three patients were randomized (34 TAMIS, 39 ESD). The ITT analysis included 33 TAMIS and 37 ESD patients after 3 post-randomization dropouts. Exclusion criteria comprised refusal to provide informed consent, inflammatory bowel disease involving the rectum, pregnancy, and severe anorectal fibrosis resulting from prior surgery. Patients were also excluded if they had granular homogeneous-type laterally spreading tumors, for which piecemeal endoscopic mucosal resection is considered standard therapy, lesions >50 mm with endoscopic features suggestive of advanced histology (NBI International Colorectal Endoscopic 3/Japan NBI Expert Team 3 or Kudo's classification type VN), or synchronous neoplasms requiring radical rectal surgery irrespective of local resection.

Intervention: Both groups (Control TAMIS and Experimental ESD) underwent bowel preparation with polyethylene glycol or sodium picosulfate. In the TAMIS arm, procedures were performed under general anesthesia in the lithotomy position using a dedicated transanal access port with carbon dioxide insufflation. Circumferential marking around the lesion was performed using electrocautery, maintaining a margin of 5 to 10 mm and resected using traction-assisted mucosal or full-thickness excision at the surgeon's discretion, followed by hemostasis and defect suturing. In the ESD arm, procedures were performed under deep sedation or general anesthesia with carbon dioxide insufflation, submucosal injection, and dissection using an electrosurgical knife; visible vessels were prophylactically coagulated, and defect closure was discretionary.

Outcomes: Primary outcome was histologically confirmed local recurrence at the resection scar 12 months after treatment. Secondary outcomes included technical success, en-bloc and R0 resection, curative resection, early local recurrence rate, procedure time, adverse events, hospital stay, and cost.

Data Analysis: Both intention-to-treat (ITT) and per-protocol analyses were performed. ESD was considered noninferior if the upper boundary of the two-sided 90% confidence interval for the recurrence-risk difference did not exceed the noninferiority margin. The noninferiority margin was set at 10%.

Funding: The study was funded by the Foundation of the Spanish Society of Gastrointestinal Endoscopy

Results: During the follow-up, no local recurrences occurred after ESD, whereas 2 recurrences occurred after TAMIS (within 6 months of the procedure). The ITT recurrence-risk difference was -6.7% (90% CI, -14.2 to 0.8), meeting the prespecified criterion for noninferiority of ESD. Technical success was 100% with ESD versus

90.9% with TAMIS in ITT analysis. Median hospital stay was shorter after ESD than TAMIS (1 vs 2 days; $P < 0.001$), and the median direct total cost was lower with ESD (€6,167.14 vs €11,289.27; $P < 0.001$). Median procedure time was longer with ESD (140 vs 110 minutes; $P = 0.02$, per-protocol). Overall, early and delayed complication rates were not statistically different.

COMMENTARY

Why Is This Important?

Rectal lesions with a risk of superficial submucosal invasion require en-bloc local resection to enable accurate histopathologic staging, assess resection margins, and determine whether additional radical surgery is necessary. In addition, in early superficial submucosal invasive rectal adenocarcinoma with favorable histologic features (depth of submucosal invasion < 1000 microns, lack of perineural and lymphovascular invasion, well to moderate differentiation and low tumor budding), an R0 resection can be considered curative. While ESD and TAMIS can both achieve en-bloc resection, prior comparative studies were largely retrospective, and DSETAMIS-2018 is a randomized controlled trial directly comparing the 2 approaches. The trial supports ESD as a potentially organ-preserving alternative to TAMIS in carefully selected early rectal neoplasms. Beyond comparable short-term local control, ESD avoided conversion to another approach, reduced hospitalization, and substantially lowered direct costs.

Key Study Findings

This randomized, noninferiority, open-

label, multicenter clinical trial comparing ESD vs TAMIS in early rectal neoplasms reported no recurrence in the ESD group, compared with 2 cases of recurrence in the TAMIS group; the trial met its prespecified noninferiority criterion for ESD. Technical success in ESD was 100%, while the TAMIS group had 90.9% ($P = 0.10$); 6 patients assigned to TAMIS underwent ESD 3 due to patient preference and 3 because the lead surgeon considered them unsuitable candidates for the procedure. En-bloc resection was high and similar with both techniques, at 97.3% with ESD and 97.0% with TAMIS in ITT analysis. Median hospital stay was shorter after ESD than TAMIS (1 vs 2 days; $P < 0.001$), and the median direct total cost was lower with ESD (€6,167.14 vs €11,289.27; $P < 0.001$). Both interventions had generally favorable safety profiles. Although differences were not statistically significant.

Caution

The noninferiority conclusion should be interpreted cautiously. The sample size of the trial was small, with 73 randomized patients and only 2 local-recurrence events, both in the TAMIS

group. The absence of recurrence events after ESD limits the precision of recurrence and recurrence-free survival estimates. Secondly, the study used a 10% noninferiority margin despite an anticipated recurrence rate of approximately 2.5% after either technique. Although the observed 90% confidence interval met the prespecified noninferiority criterion, this margin could permit an absolute recurrence difference that some patients and clinicians would consider clinically important. Third, blinding was not feasible because the endoscopic and surgical interventions required distinct procedural and perioperative pathways. To reduce potential ascertainment bias for the primary outcome, follow-up was performed by routine endoscopy-unit staff, and endoscopists and pathologists were often unaware of the preceding resection. Fourth, the population was highly selected: lesions were > 20 mm, located 3–14 cm from the anal verge, involved no more than 50% of the rectal circumference, and had no clinical suspicion of deep submucosal invasion. Therefore, the findings should not be generalized to extensive circumferential lesions, very distal lesions, or lesions with a high likelihood of deep invasion or unfavorable histology. Finally, procedures were performed by experienced operators at tertiary centers; outcomes may not translate directly to settings without substantial rectal ESD expertise, coordinated surgical backup, and expert gastrointestinal pathology.

Our Practice

Patient selection and local expertise are key factors when choosing between ESD and TAMIS. Large rectal neoplasms need special consideration because of the risk of submucosal invasion. In addition, rectal surgeries are associated with higher morbidity as compared to colon surgeries^{1,2}. Therefore, in our practice, careful optical assessment is carried out for all rectal neoplasms regardless of size to evaluate for overt (Kudo Vi) or covert features of submucosal invasive cancer (dominant nodule) before deciding on the best resection approach³. For any lesions with concern for submucosal invasion or advanced dysplasia, our preference is to perform en-bloc resection with a goal for R0 resection. En-bloc resection allows for optimal histological assessment for staging, and R0 resection (defined as a negative lateral or deep margin for dysplasia) can be curative if no high-risk pathological features are present. Favorable histological features include depth of submucosal invasion < 1000 microns, lack of perineural and lymphovascular invasion, well to moderate differentiation and low tumor budding. If an R0 resection is achieved with these favorable histological features, it is considered to be a “curative resection”. If a patient has a diagnosis of early-stage superficial rectal adenocarcinoma prior to resection, then we discuss these cases in a multidisciplinary conference to determine TAMIS vs ESD. It is

important to note that despite the growing popularity of ESD, TAMIS remains a useful alternative when ESD is not technically feasible, when local ESD expertise is unavailable, or when a surgical full-thickness excision is judged necessary. Decisions should be made in a multidisciplinary setting with advanced endoscopists, colorectal surgeons, radiologists, and gastrointestinal pathologists, particularly for lesions with a meaningful risk of covert invasive cancer^{2,3,5}

For Future Research

Larger randomized controlled trials with longer oncologic follow-up are needed to compare ESD and TAMIS for recurrence, salvage surgery, functional outcomes, quality of life, and cost-effectiveness. Future studies should include a broader spectrum of rectal lesions and should evaluate whether advanced approaches such as endoscopic intermuscular dissection can safely expand the endoscopic treatment boundary for selected superficial T1 cancers.

Conflict of Interest

Dr. Bilal is a consultant for Boston Scientific, Steris Endoscopy, Microtech, OVESCO, and Cook Medical. Dr Saeed reports no relevant conflicts of interest.

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Low-Dose Aspirin Chemoprevention in Lynch Syndrome



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This summary reviews Burn J, Borthwick GM, Elliott F, et al. Aspirin for cancer prevention in individuals with Lynch syndrome: first results from the CaPP3 multicentre, randomised, double-blind, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2026;11(9):760-774.

Correspondence to Timothy Yen, MD. Associate Editor. Email: EBGI@gi.org

Keywords: Lynch syndrome, aspirin chemoprevention, daily aspirin, cancer

STRUCTURED ABSTRACT

Question: In individuals with Lynch syndrome, is daily aspirin at 100 mg or 300 mg daily non-inferior to 600mg daily for the prevention of Lynch-syndrome associated cancers?

Design: The Cancer Prevention Programme 3 (CaPP3) trial was a multicenter, parallel-group, randomized, double-blind, dose non-inferiority trial.

Setting: The patients for the trial were from clinical genetics centers in the United Kingdom, Australia, Finland, Israel, and Spain.

Patients: Eligible participants included adults (≥ 18 years) with confirmed Lynch syndrome who carry a pathogenic variant in *MLH1*, *MSH2*, *MSH6*, or *PMS2*, whether newly diagnosed or undergoing routine cancer surveillance. Key exclusion criteria were regular, long-term nonsteroidal anti-inflammatory drug use, aspirin intolerance or sensitivity, active bleeding disorders, or other clinically significant medical illnesses.

Intervention: Participants were randomly assigned (3:3:4 ratio) to receive a daily dose of 100 mg, 300 mg, or 600 mg aspirin for a 2-year double-blind treatment phase. Following this, participants transitioned to an open-label phase of 100 mg daily via hospital prescription (75 mg in the UK due to local availability). While intervention discontinuation was permitted at any time, adherence to the 5-year treatment course was encouraged.

Outcomes: The primary outcome was the number of new mismatch-repair deficient (Lynch syndrome-associated) cancers diagnosed following intervention initiation. Secondary outcomes included the number and cumulative incidence of colorectal cancer, cancer of any organ, and 2-year blinded safety outcomes (specifically tracking adverse events such as gastrointestinal effects, bleeding, allergy, fever, hearing disturbances, and laboratory abnormalities).

Data Analysis: The primary analysis evaluated whether lower daily aspirin doses (100 mg and 300 mg) were non-inferior to 600 mg daily for cancer prevention in Lynch syndrome, determined by 2 complementary approaches: time to first cancer and overall cancer burden. Cox proportional hazards regression and Kaplan-Meier curves were used to estimate age- and sex-adjusted hazard ratios (HRs) for time to first cancer, while negative binomial regression estimated age-, sex-, and location-adjusted incidence rate ratios (IRRs) to capture overall cancer burden. Non-inferiority was declared for a lower dose if the upper bound of the 95% confidence interval for both the HR and IRR remained below 1.5 for both intention-to-treat (ITT) and per-protocol (PP) analyses.

Funding: Primarily funded by Cancer Research UK, alongside international charitable support and trial medication provided at no cost by Bayer Pharma.

Results: The ITT population consisted of 1,866 patients, and the PP population consisted of 1,136 patients who adhered through the blinded phase and consented to continue into the open-label phase at the 2-year review.

For the primary endpoint, the 300 mg aspirin group did not demonstrate non-inferiority compared to 600 mg for either time to first cancer (HR) or overall cancer burden (IRR) in both the ITT and PP populations. The 100 mg aspirin group demonstrated non-inferiority in the ITT analyses for both HR and IRR, but only for cancer burden (IRR) in the PP analysis (**Table 1**).

For the secondary endpoints, the 300 mg aspirin group failed to demonstrate non-inferiority for any outcome in either the ITT or PP analyses. For the 100 mg group, colorectal cancer burden (ITT IRR 0.85 [95% CI 0.48-1.48]) and overall cancer burden (ITT IRR 0.97 [95% CI 0.69-1.36]; PP 0.94 [95% CI 0.62-1.44]) met criteria for non-inferiority, but time to first colorectal cancer or time to first

cancer did not meet this threshold. Safety outcomes generally favored the lower aspirin dose. Although there was a numerical increase in serious adverse events with increasing aspirin dose (4.6% with 100 mg vs 6.3% with 600 mg), this was not statistically significant ($P = 0.19$). In contrast, serious bleeding events demonstrated a significant dose-response relationship, occurring in 0% of participants receiving 100 mg compared with 1.5% receiving 600 mg over 5 years ($P = 0.004$), suggesting that the principal safety concern with higher-dose aspirin is bleeding rather than an increase in serious adverse events overall.

Comparison	ITT HR (95% CI)	ITT IRR (95% CI)	PP HR (95% CI)	PP IRR (95% CI)
100 mg vs 600 mg	0.97 (0.67-1.42) ✓	0.94 (0.65-1.38)✓	1.00 (0.61-1.63)*	0.90 (0.55-1.46) ✓
300 mg vs 600 mg	1.28 (0.91-1.80) *	1.12 (0.79-1.61)*	1.42 (0.91-2.19)*	1.28 (0.82-1.98)*

Table 1. Primary endpoint of new primary Lynch syndrome (MMR-deficient) cancers, analyzed 2 ways: time-to-first-cancer (Cox HR) and cancer burden across multiple anatomical sites (negative binomial regression IRR).

✓ = non-inferiority met

* = non-inferiority not met

CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratios; ITT, intention to treat; MMR, mismatch repair; PP, per-protocol.

COMMENTARY

Why Is This Important?

The CaPP3 trial is the long-awaited follow-up to the landmark CaPP2 trial,¹ which established aspirin as an effective chemopreventive agent in Lynch syndrome. In CaPP2, participants randomized to 600 mg of aspirin daily experienced a significantly lower risk of colorectal cancer than those receiving placebo (HR 0.65, 95% CI 0.43-0.97; $P = 0.035$). While CaPP2 demonstrated the efficacy of aspirin in reducing cancer risk, adoption of the 600 mg dose has been limited by concerns regarding

bleeding risk and long-term tolerability. For example, a 2017 survey of general practitioners found that only 62% were willing to prescribe 600 mg daily, compared with 91% who would prescribe 100 mg.²

Although CaPP3 did not formally demonstrate non-inferiority of either 100 mg or 300 mg aspirin compared with 600 mg, potentially due to suboptimal follow-up duration up to 8 years, the overall findings are very encouraging.

As demonstrated in the study, both 600 mg and 300 mg (typically 325 mg) doses of aspirin can cause side effects such as bleeding and gastrointestinal discomfort. In our experience, patients largely tolerate “baby” aspirin (81 mg in the United States rather than 100 mg) very well, particularly in younger individuals who are otherwise healthy.

Key Study Findings

Although the 100 mg aspirin dose did not formally meet criteria for non-inferiority, effect estimates were similar to higher doses. Given the favorable adverse effect profile of low-dose aspirin, an 100 mg (or 81 mg) dose of aspirin is a reasonable option for cancer prophylaxis in Lynch syndrome patients.

Caution

Although the study results did not meet non-inferiority thresholds, the median follow-up of 5.5 years was relatively short compared to the 20+ year follow-up of CAPP2. Subsequent follow-up studies could potentially narrow confidence intervals below the non-inferiority threshold if there truly is no significant difference in efficacy with lower aspirin doses.

It is also important to note that this study may not address the role of low-dose aspirin in *PMS2* Lynch syndrome patients or obese patients. *PMS2* Lynch syndrome patients were under-represented in CAPP3, as it has been historically in other large-scale studies.³

CAPP3 was also under-powered to account for obesity, which is important because individuals with obesity may require higher aspirin doses.⁴

Our Practice

In our practice, we routinely discuss aspirin chemoprevention with individuals with Lynch syndrome, although this is not a one-size-fits-all recommendation. Low-dose 81 mg aspirin daily is a reasonable choice for those prone to peptic ulcer disease or bleeding. This increased bleeding risk can be seen not only in those with other medical comorbidities, but also young, otherwise healthy Lynch syndrome patients who engage in contact sports.⁵ In addition, the chemopreventive benefit of aspirin may not emerge for 5-10 years after initiation. Therefore, we are less likely to initiate aspirin in adults age 70 and up whose risk of bleeding often outweighs any delayed cancer preventative benefit that they would receive at that age.¹ We also counsel patients that the demonstrated benefit of aspirin depends on consistent long-term use, and that aspirin should be viewed as an adjunct to guidelines based surveillance colonoscopy.⁶ For example, in this study 5%-10% of participants still developed colorectal cancer over a relatively short time frame regardless of aspirin dose.

For Future Research

In addition to longer follow-up of the CaPP3 cohort to refine non-inferiority analyses of lower aspirin dosages, future

studies should investigate the impact of aspirin in the context of other risk-modifiers such as obesity, prior cancer history, and colonoscopy (or other risk-reduction modalities). Finally, the role of aspirin in cancer chemoprevention may also change depending on the results of ongoing vaccine trials against Lynch-syndrome associated cancers.⁷

Conflict of Interest

The authors of the summary declare no conflicts of interest.

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Family-Based Obesity Treatment in Primary Care: An Upstream Strategy for Metabolic and Liver Health



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This summary reviews Staiano AE, Cook SR, Stein RI, et al. Family-centered child obesity treatment: the TEAM UP randomized clinical trial. JAMA Pediatr. 2026. doi:10.1001/jamapediatrics.2026.3067.

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Keywords: Childhood obesity, family-based behavioral treatment, primary care, pediatric obesity, metabolic health, percent median BMI

STRUCTURED ABSTRACT

Question: Among children and adolescents with obesity receiving care in primary care practices, does adding family-based behavioral treatment (FBT) to enhanced standard of care (ESOC) improve weight outcomes compared with ESOC alone?

Design: The study was a pragmatic, multicenter, comparative-effectiveness randomized clinical trial conducted from 2019 to 2024, with blinded outcome assessment and follow-up through 18 months.

Setting: The trial was conducted in 41 primary care clinical practices in Louisiana, New York, Missouri, and Illinois, reflecting real-world pediatric obesity care.

Patients: A total of 730 parent-child dyads were randomized. Eligible children

were aged 6 to 15 years with obesity, defined as body mass index at or above the 95th percentile for age and sex. The cohort was socioeconomically diverse: 46.6% were insured by Medicaid and 22.1% lived in households reporting food insecurity. Children with significant eating disorder symptoms or medical conditions substantially affecting growth, appetite, weight, or physical activity were excluded.

Intervention: All participants received ESOC, a primary care practitioner-led obesity management program based on American Academy of Pediatrics guidance and intensified according to clinical response over 12 months. The intervention group additionally received structured FBT delivered by trained interventionists, emphasizing healthy eating, physical activity, behavioral self-management, positive parenting strategies, and modification of home and social environments.

Outcomes: The primary outcome was change in percent over median body mass index (BMI), or percent median BMI, from baseline to 12 months. Secondary and exploratory outcomes included additional BMI metrics, the proportion achieving a clinically meaningful BMI z-score reduction of at least 0.25, child and parent-reported quality of life, cardiometabolic measures, parent weight change, and adverse events.

Data Analysis: Analyses were conducted using an intention-to-treat framework. Linear mixed-effects models evaluated treatment effects while adjusting for site, child age, sex, and race. Completer, tipping-point, and preplanned sensitivity analyses were performed to assess robustness.

Funding: The trial was funded primarily by the Patient-Centered Outcomes Research Institute, with additional institutional and National Institutes of Health support. Funders had no role in study design, conduct, or reporting.

Results: Among 723 analyzed participants, mean age was 10.8 years, 53.5% were female, 46.6% were insured by Medicaid, and 22.1% lived in households with food insecurity. At 12 months, children receiving ESOC+FBT achieved a significantly greater reduction in percent median BMI than those receiving ESOC alone, with a between-group difference of -3.8 units (95% CI, -6.20 to -1.34; $P = 0.002$). Benefits were evident by 6 months and persisted through 18 months, with a between-group difference of -4.3 units at 18 months (95% CI, -7.25 to -1.41). Nearly half of ESOC+FBT children met the clinically meaningful BMI z-score reduction threshold at 18 months, and weight-related quality of life improved more in the ESOC+FBT group at the end of treatment. No adverse events were deemed related to trial participation.

In this pragmatic primary care trial, adding family-based behavioral treatment to enhanced standard obesity care produced greater and more durable reductions in

relative weight than enhanced standard care alone. These findings demonstrate that evidence-based, family-centered obesity treatment can be implemented in routine primary care settings serving geographically and socioeconomically diverse populations. For gastroenterology (GI) and hepatology clinicians, the study supports earlier intervention on pediatric obesity before obesity-related metabolic and liver complications become established.

RCT: Family-Centered Child Obesity Treatment

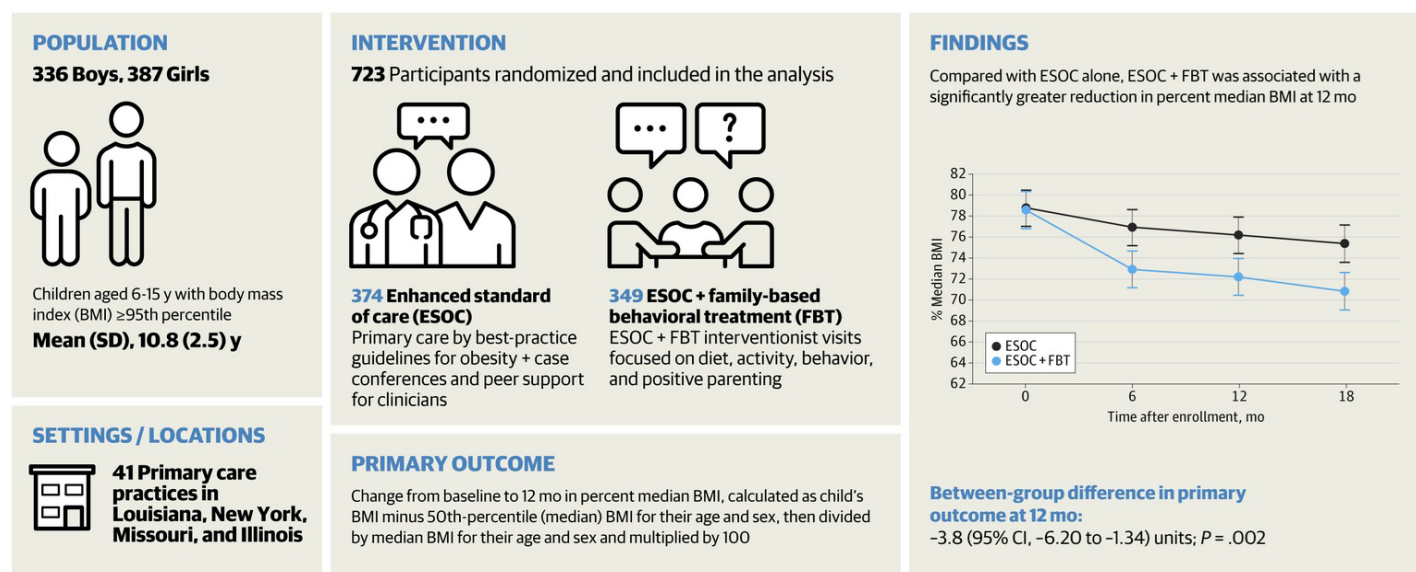


Figure 1. Visual abstract for RCT: Family-centered child obesity treatment.

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COMMENTARY

Why Is This Important?

Childhood obesity affects approximately 1 in 5 US children and adolescents and is an upstream driver of cardiometabolic disease, impaired quality of life, and future obesity-related liver disease.¹ For gastroenterologists and hepatologists, childhood obesity is not only a pediatric primary-care issue; it is an early determinant of metabolic dysfunction-associated steatotic liver disease (MASLD), cardiometabolic risk, and future adult digestive disease burden. TEAM UP is therefore relevant to GI practice because it tests whether an

evidence-based obesity intervention can be delivered earlier, closer to where families receive routine care, and before obesity-related liver and metabolic complications become entrenched.

The 2023 AAP clinical practice guideline recommends intensive health behavior and lifestyle treatment, including at least 26 contact hours over 3 to 12 months, for children aged 6 years and older with obesity.^{2,3} Family-based behavioral treatment is a well-validated example of this approach,^{4,5} but it has historically been delivered in specialty research clinics and

remains unavailable to many families. TEAM UP addresses a pragmatic and policy-relevant question: can structured FBT be embedded within primary care and still produce meaningful benefit in a geographically and socioeconomically diverse population?

The trial is especially important because it included 41 real-world primary care practices and enrolled a broad population, including nearly half of children insured by Medicaid and more than 1 in 5 from households experiencing food insecurity. This makes the findings more relevant to routine pediatric obesity care than many efficacy trials conducted in specialized academic settings.

Key Study Findings

In this pragmatic randomized trial of 730 children aged 6 to 15 years across 41 primary care practices, adding FBT to ESOC reduced percent median BMI by 3.8 units more than ESOC alone at 12 months, with persistence of benefit at 18 months. Nearly half of children receiving ESOC+FBT achieved a clinically meaningful BMI z-score reduction by 18 months. Both treatment arms improved relative weight and quality of life, but the addition of FBT produced greater benefit, supporting the value of structured family-centered behavioral treatment when it can be delivered in primary care.

The trial also demonstrates that meaningful pediatric obesity treatment need not be confined to specialty centers.

ESOC+FBT was delivered in primary care settings, with trained interventionists focusing on healthy eating, physical activity, positive parenting, behavioral skills, and management of social and environmental cues. For GI clinicians, the message is upstream prevention: earlier, family-centered obesity treatment may help reduce later metabolic and liver disease burden.

Caution

Several features temper interpretation. Enrollment and treatment delivery were disrupted by the COVID-19 pandemic, prompting a mid-trial reduction in target sample size from 1,296 to 728 dyads. The study retained power for the primary endpoint but not for prespecified race-by-sex interaction analyses.

Treatment dose is also central to interpretation. Although 26 to 33 FBT sessions were planned,^{3,6} mean attendance was 16.7 sessions, and attendance was lower among African American children, Medicaid-insured children, and families with food insecurity. This cuts both ways: the observed effect is impressive despite incomplete treatment exposure, but real-world uptake barriers may limit population-level impact if flexible delivery models are not built into implementation. The attendance pattern should be interpreted as evidence of structural barriers, not as lack of family motivation.

ESOC was also an enhanced, trained,

guideline-based comparison condition rather than ordinary unstructured primary care, so the incremental benefit of FBT should not be interpreted as a comparison against minimal care. The primary outcome was a relative-weight measure over 12 months rather than a hard cardiometabolic or long-term liver endpoint, and most secondary outcomes were exploratory and not adjusted for multiplicity. Height and weight were sometimes collected remotely or extracted from the medical record, representing about 21% of follow-up data, although a within-trial validation study supported concordance. Finally, families were referred by their primary care practitioner or self-selected into the trial, which may limit generalizability to less motivated or less connected populations.

Our Practice

In GI and hepatology practice, TEAM UP reinforces the importance of treating pediatric obesity as an early, modifiable risk factor for future metabolic and liver disease rather than waiting until adolescents present with established MASLD or cardiometabolic complications.^{7,8} When counseling families, we emphasize that intensive behavioral treatment is not simply “diet advice.” In TEAM UP, FBT included structured nutrition and physical activity plans, positive parenting, self-monitoring, goal setting, problem-solving, and attention to the home and social environment.

Engagement is a clinical problem to solve rather than a patient or family failing. The lower attendance observed among African American children, Medicaid-insured children, and families with food insecurity suggests that clinicians should treat missed visits as a signal of structural barriers. In practice, that means screening for social needs, offering telehealth and flexible scheduling when feasible, coordinating with primary care and behavioral health teams, and advocating for reimbursement models that make intensive behavioral treatment accessible. Telehealth and flexible delivery deserve particular attention because the draft notes that better attendance and outcomes were associated with flexible approaches.

For adolescents with more severe obesity or comorbidities, pharmacologic adjuncts, including glucagon-like peptide-1 receptor agonists, may be relevant complements to intensive behavioral treatment. However, TEAM UP reinforces that behavioral treatment remains foundational and should not be displaced by medication alone.⁹ I would frame the clinical goal as improving health trajectories, quality of life, and future metabolic and liver risk, while remaining attentive to weight stigma and emerging disordered eating concerns.

For Future Research

Future research should test scalable implementation models that embed FBT into routine primary care while

reducing attendance gaps for families facing structural barriers. Head-to-head comparisons of telehealth, hybrid, and in-person delivery models are needed to determine how to optimize engagement without diluting treatment effects.

GI-relevant future studies should assess whether early family-based obesity treatment reduces incident MASLD, improves liver enzymes or imaging-based steatosis and fibrosis measures, and delays or prevents adolescent referral for obesity-related liver disease. Longer-term follow-up is also needed to assess durability of weight change, cardiometabolic outcomes, quality of life, and the best sequencing or combination of intensive behavioral treatment with pharmacotherapy. Multidisciplinary care models linking primary care, gastroenterology/hepatology, nutrition, behavioral health, and community support may be especially important for translating TEAM UP from trial evidence into population health benefit.

Conflict of Interest

The authors of the summary declare no conflicts of interest.

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Phase 3 Results of Bepirovirsen Treatment for Chronic Hepatitis B Virus Infection Allow Up to 20% of Treated Individuals to Discontinue All Hepatitis B Therapies

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This summary reviews Hou J, Lim SG, Buti M, et al. Phase 3 Results of Bepirovirsen Treatment for Chronic Hepatitis B Virus Infection. *N Engl J Med.* 2026;394(24):2395-2406.

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LIVER

STRUCTURED ABSTRACT

Question: Can a 24-week finite course of subcutaneous bepirovirsen, an anti-sense oligonucleotide that targets all hepatitis B virus (HBV) transcripts, safely and effectively induce a functional cure in adults with chronic HBV infection who are currently virologically suppressed on stable nucleoside or nucleotide analogue (NA) therapy, allowing up to 20% of individuals to safely discontinue treatment for hepatitis B?

Design: Two identical, duplicate-design, phase 3, multicenter, randomized, double-blind, placebo-controlled trials (B-Well 1 and B-Well 2).

Setting: The trial was conducted internationally across 29 countries spanning Europe, the Asia-Pacific region, and the Americas.

Patients: A total of 1,838 randomized adults (1,834 in the full analysis population) with documented noncirrhotic chronic HBV infection. Eligible patients had been on stable NA therapy for 6 months, with baseline HBV DNA < 90 IU/mL, alanine aminotransferase (ALT) < 2 times upper limit of normal and baseline HBsAg levels > 100 and < 3,000 IU/mL.

Exposure: Patients randomized in a 2:1 ratio to receive either weekly subcutaneous injections of bepirovirsen (300 mg, plus loading doses on days 4 and 11) or a matching placebo for 24 weeks. All patients maintained background NA therapy through week 48. Those who met strict virologic response criteria discontinued NA therapy at week 48.

Outcomes: *Primary endpoint:* Functional cure at week 72 (24 weeks off all HBV therapies), defined as a sustained HBV DNA level below the lower limit of quantification (LLOQ) < 20 IU/mL or not detected), qualitative HBsAg loss (< 0.05 IU/mL), and no use of rescue medication. *Key secondary endpoints:* Functional cure rate in the lower baseline HBsAg stratum (< 1,000 IU/mL); proportion of patients maintaining sustained HBV DNA < LLOQ at week 72 after stopping NAs in the overall population and the lower HBsAg stratum.

Data Analysis: Efficacy analyses were performed on the full analysis set. Missing data that prevented efficacy assessment were imputed as nonresponse.

Funding: The trial was funded by GlaxoSmithKline.

Results: Bepirovirsen achieved a functional cure at week 72 in 20% of patients in B-Well 1 (127/650) and 19% in B-Well 2 (106/570), compared to 0% in both placebo groups ($P < 0.001$). Functional cure was significantly higher in patients with baseline < HBsAg 1000IU/mL, reaching 25% in B-Well 1 and 28% in B-Well 2 ($P < 0.001$). In the higher stratum (>1,000 to 3,000 IU/mL), cure rates were 10% and 5%, respectively.

Post-NA discontinuation viral suppression HBV DNA < LLOQ at week 72 was sustained in 23% of bepirovirsen patients across both trials.

In a pooled analysis, active treatment period (weeks 1–24) adverse events occurred in 89% of the bepirovirsen group vs 65% for placebo. Grade 3 adverse events occurred in 16% of bepirovirsen patients, most commonly presenting as a transient ALT flare (6%). Reversible, treatment-dependent reductions in platelet counts and eGFR were observed, which returned toward baseline off therapy.

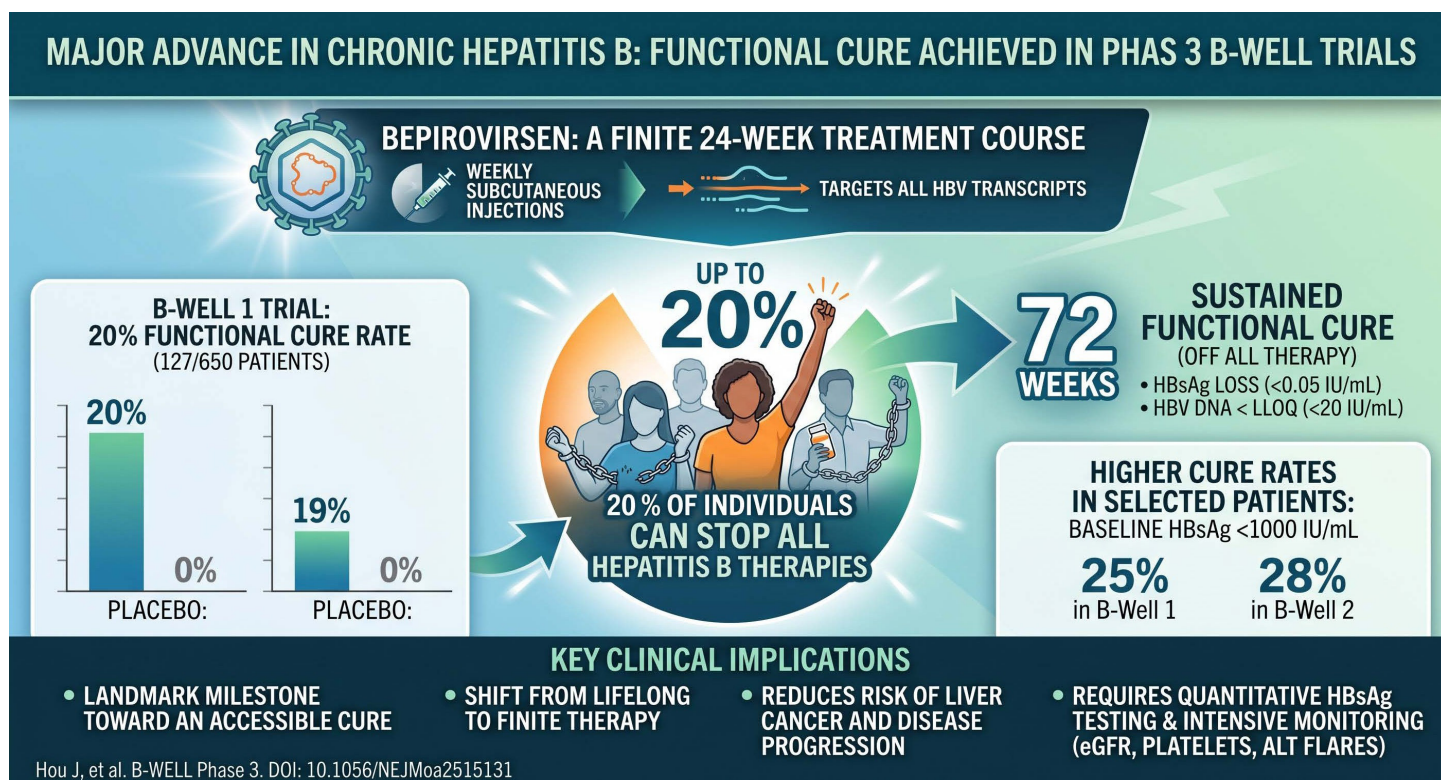


Figure 1. Visual summary.

COMMENTARY

Why Is This Important?

Standard oral nucleoside/NA therapies are highly effective at suppressing HBV replication, but they rarely lead to the loss of hepatitis B surface antigen (HBsAg), meaning patients typically face lifelong therapy. A functional cure, characterized by sustained undetectable HBsAg and HBV DNA off treatment, dramatically lowers the risk of developing hepatocellular carcinoma, halts progression of the disease, and removes the continuous burden, financial costs, and adherence risks of lifelong suppressive medication. The B-Well phase 3 trials represent a landmark milestone toward an accessible cure. By adding just 1 investigational agent (bepirovirsen) for a

fixed 24-week duration, nearly a fifth of selected patients achieved a functional cure and completely freed themselves from baseline background therapy. The B-Well phase 3 trials represent a significant milestone toward an accessible cure of hepatitis B. By adding a single investigational agent (bepirovirsen) for a fixed 24-week duration, nearly a fifth of selected patients achieved a functional cure and completely freed themselves from baseline background therapy.

Key Study Findings

Bepirovirsen demonstrated robust replication of efficacy across 2 major international trial populations, showing

overall functional cure rates of 19% to 20%. Baseline quantitative HBsAg stratification dramatically changed response rates: a lower baseline antigen load <1,000 IU/mL translated into functional cure rates as high as 28%. Additionally, anti-HBs seroconversion developed in roughly two-thirds of the patients who achieved a functional cure in a post hoc analysis. From a safety perspective, transient ALT increases of at least 3X upper limit of normal occurred in 24% of patients during active treatment, aligning closely with rapid immunomodulatory clearance of systemic HBsAg rather than true drug-induced liver injury.

Caution

While these results are highly encouraging, clinical limitations remain. The current efficacy profiles cannot be generalized to patients outside the trial design criteria, specifically those with advanced cirrhosis, coinfections (HIV, hepatitis C virus, or hepatitis D virus), or high baseline surface antigen levels (>3,000 IU/ml). Furthermore, antisense oligonucleotides carry known class side effects. Active therapy requires rigorous clinical and laboratory surveillance due to a 16% incidence of Grade 3 adverse events (most commonly increased ALT levels) and temporary, drug-induced declines in estimated glomerular filtration rate (eGFR) and platelet counts. There was close monitoring in the trial (every 1-2 weeks), and a similar approach will be required in practice.

My Practice

The potential introduction of bepirovirsen as an option to achieve functional cure will change my practice and the practice of those who care for those with chronic hepatitis B substantially. For selected individuals now, there will be an option to transition individuals who previously committed to lifelong nucleoside/nucleotide analog therapy to the potential for a finite treatment with an approximately 20% chance to safely and permanently discontinue treatment. While at Stanford, our HBsAg automatically reflexes to a quantitative index (signal of the cutoff ratio) to give an approximate quantitative level, we will now need to adopt quantitative surface antigen testing to identify ideal candidates for this treatment (less than or equal to 1,000 international units/mL) as they exhibit the highest clinical response with functional cure rates reaching 25% to 28%. While oral NAs are well tolerated with minimal monitoring, bepirovirsen will require more intensive laboratory monitoring, and our practice will adapt by performing regular blood work every 1 to 2 weeks, depending on the monitoring guidance. We will need to monitor platelet counts and renal function (eGFR), and we will gain further experience managing ALT flares, which signal immune-mediated clearance of infected cells. We will also need to establish strict milestones to determine who can successfully stop their NA therapy, which will mirror the trial where loss of hepatitis B surface

antigen from week 24-46 can proceed with discontinuation of NA therapy at week 48 and an evaluation of functional cure at week 72.

For Future Research

To optimize the real-world utility of bepirovirsen, future prospective research must establish the true durability of this functional cure over extended, multi-year timelines. Moreover, bepirovirsen will likely serve as the backbone on which other combination therapy strategies are designed to push functional cure rates beyond the 20% mark and expand functional curative options for a wider hepatitis B population. Investigating sequential or combination therapies will be crucial.

Conflict of Interest

The author of the summary declares no conflicts of interest.