CALCULATING RISK

How Important are CRC Risk Factors and the Scores that are Based on Them?

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**Personalized Medicine: Improving on “average-risk” CRC screening**

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Dr. Imperiale has no conflicts to disclose.

In his 2015 State of the Union Address, President Obama launched the era of precision medicine, which proposes medical decisions and practices tailored to the individual patient. While the concept of precision medicine is not new, what is new is the broader scope in which precision medicine will eventually apply. Broader application of precision medicine will soon be possible because of new and powerful tools of molecular biology, genomics and bioinformatics. The near-term focus of precision medicine is on tailoring cancer treatment based largely on genetic and molecular profiling, but concepts of precision medicine will likely require consideration of combinations of several genetic, proteomic, phenotypic and other features when attempting to optimize whether and how an individual patient is screened for a particular disease, or when deciding on a diagnostic test or drug for a suspected or established diagnosis, with the goal of maximizing clinical benefit, minimizing risk of adverse effects or both. Although the recent-term focus of precision medicine is on tailoring cancer treatment based largely on genetic and molecular profiling, concepts of precision medicine will soon be possible because of new and powerful tools of molecular biology, genomics and bioinformatics.

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Dr. Lieberman has no conflicts to disclose.

As appealing as it seems, precision medicine will complicate the delivery of health care. Providers will need to consider much more information than they currently do in order to personalize prevention, diagnosis, treatment and prognosis. Simple is the example of how a single genetic mutation (in the KRAS gene) determines whether anti-EGF therapy is useful in the treatment of advanced stage colorectal cancer (CRC). Broader use of precision medicine will likely require consideration of combinations of several genetic, proteomic, phenotypic and other features when attempting to optimize whether and how an individual patient is screened for a particular disease, or when deciding on a diagnostic test or drug for a suspected or established diagnosis, with the goal of maximizing clinical benefit, minimizing risk of adverse effects or both. Although the near-term focus of precision medicine is on tailoring cancer treatment based largely on genetic and molecular profiling, concepts of precision medicine will soon be possible because of new and powerful tools of molecular biology, genomics and bioinformatics.

**CRC Risk Scores Not a Necessity for GI Practice**

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**How Important are CRC Risk Factors and the Scores that are Based on Them?**

Colors and cancer (CRC) remains the second leading cause of cancer death in North America. It would be wonderful if we could accurately measure a risk score for CRC based on a few simple questions, and use this score to determine most appropriate timing and type of screening. Unfortunately, I do not think the scores are sufficiently discriminant.

**COLON CANCER:**

Robertson et al. generated a risk scoring system and estimated the likelihood of detecting advanced neoplasia to be 1.32 percent for a score of 0 and more than 19 percent for patients with scores of 7 to 8. Imperiale et al. found the risk increased from 1.92 percent in people with a very low risk (score 0), to 24.9 percent in high-risk groups (score greater than 6). However, no one ever escapes risk if they live long enough, because age alone adds points every five years after age 50 (1) or 55 (2). Since most patients will have one or more points, they will likely fall into the middle range with rates of advanced neoplasia at 5 percent or more. No male is ever in the very lowest risk group, which limits the usefulness of the current risk scoring systems for men. These scores and their validation remind us that risk of advanced neoplasia and CRC is complicated, and may vary based on many factors. Not included in the U.S. and Polish models is the use of aspirin or NSAIDs, known to reduce risk of recurrent adenomas, incidence of CRC and the mortality of CRC. The Polish study applies to Caucasians only. The U.S. studies do not include race or ethnicity as variables in the model. Since black men and women in the U.S. may have a higher risk of advanced lesions compared to age-matched whites, it is not clear if such scoring would apply to blacks.

**NOT A NECESSITY - CONTINUED ON PAGE 6**

Investigators from Poland and the U.S. have recently published and validated risk scores aimed at stratification of risk for colorectal cancer by primary care providers. The elements are similar in all three studies — including age, sex, smoking history, BMI or waist circumference, and family history of CRC. These risk scores are designed to include data that is readily available to a primary care provider. A more complex German scoring system includes non-steroidal anti-inflammatory drugs (NSAID) use, prior colonoscopy (and polyps) and red meat consumption. Results of such stratification could be used to customize screening — provided that the scores was sensitive enough. Kaminski et al. generated a risk scoring system and estimated the likelihood of detecting advanced neoplasia to be 1.32 percent for a score of 0 and more than 19 percent for patients with scores of 7 to 8. Imperiale et al. found the risk increased from 1.92 percent in people with a very low risk (score 0), to 24.9 percent in high-risk groups (score greater than 6). However, no one ever escapes risk if they live long enough, because age alone adds points every five years after age 50 (1) or 55 (2). Since most patients will have one or more points, they will likely fall into the middle range with rates of advanced neoplasia at 5 percent or more. No male is ever in the very lowest risk group, which limits the usefulness of the current risk scoring systems for men. These scores and their validation remind us that risk of advanced neoplasia and CRC is complicated, and may vary based on many factors. Not included in the U.S. and Polish models is the use of aspirin or NSAIDs, known to reduce risk of recurrent adenomas, incidence of CRC and the mortality of CRC. The Polish study applies to Caucasians only. The U.S. studies do not include race or ethnicity as variables in the model. 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established risk factors for CRC, but these are not used for making decisions about screening despite their well-known effects. For example, neither age nor sex is used, despite the fact that CRC risk nearly doubles each decade between ages 50 and 60, and that a man’s CRC risk is nearly twice that of a woman’s at any age. Among the reasons given for this non-use are a way of consider multiple risk factors simultaneously, lack of time for provider-patient discussion about the tradeoffs among screening strategies, and the fear of further “complicating” screening recommendations, confusing providers and patients.

Current screening recommendations in the U.S., are basically anything. They may be distilled to this: in the absence of a high-risk family history, men and women should be screened at age 50 with either a colonoscopy every 10 years or high-sensitivity stool occult blood test annually. These two screening strategies, and the fear of further misperception that they are “average-risk” or possibly due to one or more rounds of false-negative non-invasive testing, may improve the yield and efficiency of screening colonoscopy, optimizing use of an expensive and limited resource that is not without risk.

Models for CRC screening are meant to aid clinical judgment and decision making, not substitute for it. Like all tools in gastroenterology, none of the models are perfect, but all have shown some degree of scientific rigor. The best-performing ones are determined by both model metrics and clinical judgment — and can and should be used in person/populations comparable to those used in model development and validation. Personalized risk information may engage patients and providers into a discussion that considers risk and preferences, allows providers to make a supportive recommendation for non-average-risk individuals, and could be a more data-driven one for colonoscopy. After all, we are in the era of precision medicine, where several domains of risk factors will soon require consideration. If we can’t handle individualizing screening decisions based on a few phenotypic and behavioral features (along with patient preferences), how will we ever handle fully-implemented precision medicine?

A low score could provide patients a false sense of reassurance, and could impact rates of screening in the future.

Patients may believe they are low risk for life, and might avoid screening. Such is the case, since everyone will earn points with age and eventually move to at least the middle range for risk. Once patients reach age 55 to 60, they will no longer be in the lowest risk group, so the score may no longer be useful for risk stratification.

What is clear from these scoring systems and other data is that a 50- to 54-year-old white or Hispanic woman who is a non-smoker and has no family history of CRC has a very low risk of advanced neoplasia. When combined with 5 years, age 54, average-risk white and Hispanic women do not have a similar risk of advanced neoplasia until after age 60. If we adopted screening strategies based on risk, we would definitely recommend performing in risk white and Hispanic women until age 55. This approach might be simpler than trying to create a low-risk group.

The published data on risk scoring systems provides little evidence that such scoring systems could be applied to surveillance after initial colonoscopy. Once patients have adenomas, they clearly have whatever genetic or lifestyle factors might predispose one to colon neoplasia. Risk factors during surveillance appear to be most closely related to the pathology at the baseline colonoscopy, irrespective of these other factors.

It would be wonderful to have a precise form of risk stratification for CRC based on clinical criteria, but I am not sure the currently available scoring systems meet this benchmark. The colorectal risk scores do provide an opportunity to engage patients in informed decision making about CRC screening. However, even without a score, we know that male sex, advancing age, smoking and obesity place patients into a higher risk group, for whom screening should be strongly recommended. Young (50- to 54-year-old) white and Hispanic women fall into a very low risk group, for whom the benefits of screening should be fully elucidated. Everyone else falls into the middle range of risk. I am not sure we need a scoring system to tell us this.

Not a necessity — continued from page 5

I can see several ways in which a scoring system might be useful to primary care providers at the initiation of screening at age 50. First, it would help the primary care provider to identify the higher-risk patients who should definitely be urged to undergo colonoscopy. The high-risk groups have advanced adenoma rates of more than 15% or future risk for CRC. These multivariable models were developed and validated with comparable methods and on large numbers of average-risk persons from eastern Asia, China, Korea, Germany, Spain, Poland, and the U.S., the majority of whom had no previous screening. It is important to realize that these tools are applied initial, not subsequent, screening, as prior test results – either positive or negative – affect subsequent risk. All models include age and sex; many of them include cigarette smoking, family history of colorectal cancer, and presence of any previous abnormal screening test (body mass index or waist circumference), suggesting that these variables are both valid and generalizable. Model performance (discrimination, and the degree of clinically-significant risk stratification — varies widely and robustly, but whether the risk estimates are clinically important and distinct enough to affect the choice of screening strategy for patients and whether the low-risk estimates are clinically important is challenging and difficult to affect the choice of screening strategy. For example, if told they are low risk, some patients may believe they are low risk for life, and might avoid screening. Such is the case, since everyone will earn points with age and eventually move to at least the middle range for risk. Once patients reach age 55 to 60, they will no longer be in the lowest risk group, so the score may no longer be useful for risk stratification.

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A score to estimate the likelihood of detecting advanced colorectal neoplasms who should undergo colonoscopy. The Mayo Clinic Score: a validated tool to estimate the likelihood of advanced colorectal neoplasms in asymptomatic Asik people. Gut 2011;60(6):815-21.


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CIRCULATING TUMOR CELLS

HOW CLOSE ARE WE?

Over the past decade significant advances have been made in the development of non-invasive tools for diagnosing and monitoring treatment in a variety of solid cancers. While traditional imaging modalities and tissue biopsies are still the gold standards for establishing a cancer diagnosis, it has become apparent that these tools are ineffective at identifying cancers before they have metastasized. They are also ineffective at providing a complete picture of the complex genetic landscape present in most tumors, which is required to properly design and gauge the efficacy of treatments. In recent years, the detection of cancer cells in the circulation has emerged as a promising new technology in the fight against cancer. Analysis of these circulating tumor cells (or CTCs) allows physicians to obtain “liquid biopsies” of the tumor which have the potential to provide real-time information on treatment responses, detect early relapse and serve as a biomarker for early detection.

Circulating tumor cells are released into the bloodstream from a tumor and allow us to scrutinize the biology of a tumor without performing invasive biopsies. The central challenge in isolating CTCs is their rarity in the circulation, with an estimated one to 10 cells per billion normal blood cells in 1 ml of blood. To find these ultra-rare cells, current technologies employ one of two approaches: (1) Positive selection, which entails capturing CTCs based on their physical properties or (2) Negative selection, whereby depletion of red Blood Cells and White Blood Cells from blood samples results in a purified CTC population.

Methodologies aimed at detecting CTCs based on physical properties often rely on the presence of specific cell surface markers or differences in the cell size, electric charge or density of CTCs compared to surrounding leukocytes. Currently, the only FDA-approved CTC technology, CellSearch, utilizes magnetically tagged antibodies to the common epithelial cell surface marker EpCAM to capture tumor cells from the blood of cancer patients. This approach has been used to demonstrate the utility of CTCs as prognostic markers of survival and treatment response in metastatic breast, prostate and colon cancer.1 However, the broad applicability of the CellSearch system continues to be limited due to the low recovery rates for CTCs, as a result of the multiple processing steps, and the fact that the system often only detects CTCs in half of patients with metastatic disease.

In an effort to increase both the sensitivity and purity of CTC capture, biomimicking approaches using microfluidic-based technologies have been developed. Using methods originally developed for manufacturing microprocessors, we can now fabricate devices with microscopic channels coated with antibodies that can capture tumor cells directly from whole blood with minimal processing. Early studies using these “CTC-Chip” platforms show promise in detecting even small numbers of CTCs in patient samples, which can also be subjected to detailed molecular analysis.2 However, a significant limitation of all positive enrichment approaches is their reliance on tumor-cell-specific factors for isolation. It is increasingly recognized that CTCs are quite heterogeneous, coming in all shapes and sizes, and often expressing many different surface epitopes. This can make detection using a specific marker challenging.

Negative selection approaches attempt to resolve this issue using marker-agnostic methods to isolate CTCs. They are based on the premise that while CTCs may not be uniform in their expression of surface markers, leukocytes all invariably express certain well-characterized proteins. Using magnetically coated antibodies to standard leukocyte markers such as CD45, it is now possible to enrich for CTCs by depleting non-tumor cells from blood specimens. Initial results from limited patient cohorts are promising and demonstrate the ability to detect CTCs in nearly all patients with metastasis. Importantly this approach can also detect tumor microemboli (i.e. clusters of tumor cells) in the circulation, which are often associated with increased metastatic burden3 and lower patient survival.

As CTC technologies continue to evolve, they will significantly improve our ability to diagnose and treat solid cancers. As CTC technologies continue to evolve, they will significantly improve our ability to diagnose and treat solid cancers. As CTC technologies continue to evolve, they will significantly improve our ability to diagnose and treat solid cancers. As CTC technologies continue to evolve, they will significantly improve our ability to diagnose and treat solid cancers.
ERGONOMICS AND ENDOSCOPIC RELATED INJURIES

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The assessment and prevention of work-related injury to physicians who perform endoscopy is a remarkably understudied area, but an extremely important one. Endoscopists are at risk of musculoskeletal strain and repetitive motion injury due to procedures requiring repetitive push-and-pull movements of the arms, torquing of the endoscope with force, and a prolonged grip of the control dials. Endoscope design contributes to strain on the gastroenterologist. In addition, endoscopists often work in awkward postures while manipulating the scope, and factors such as suboptimal monitor position and bed height can aggravate neck and back strain.

An ASGE technology report estimates the prevalence of musculoskeletal symptoms in gastroenterologists to be from 37 percent up to 89 percent.1 Skeletal muscle complaints are more common in gastroenterologists than in other internal medicine specialists. A number of surveys have linked musculoskeletal injuries to a high-volume endoscopy practice. According to a recent study, gastroenterologists performing more than 20 endoscopies per week are at risk of endoscopy-related injuries.2

The Occupational Repetitive Actions (OCRA) index is an ergonomic risk assessment tool; it estimates that about 10 percent of endoscopists will develop upper extremity musculoskeletal injury after 10 years of performing endoscopic procedures. Overuse injuries occur due to repeated microtrauma to a tendon or ligament, or from ischemia to peripheral nerves.3

The most common injuries reported by endoscopists are carpal tunnel syndrome, pain in the left thumb, the right wrist, the cervical spine and the lower back. A “colonoscopist’s thumb” is De Quervain’s tenosynovitis of the left thumb due to repetitive strain from controlling the endoscope dials. A “biliary endoscopist’s knuckle” is injury to the metacarpophalangeal joint and results from making a forceful pinch grip and advancing biliary, endoscopic instruments and devices, through biliary strictures.4

In my practice at a tertiary care cancer hospital, about 1,100 to 1,200 endoscopies are performed monthly. A number of endoscopic procedures are complex and time consuming, reflective of our patient population. Patients may require treatment of malignant biliary obstruction, control of bleeding in thrombocytopenic patients, tumor staging and ablation, high-volume screening and surveillance endoscopy is also performed. There are 14 full-time gastroenterologists, 11 of whom spend 22 hours or more per week in the endoscopy unit. In the past two years, three of the 11 endoscopists who spend half their time or more performing endoscopic procedures have required prolonged leave of absence due to musculoskeletal injuries of the spine and upper extremities. These injuries are most likely related to chronic overuse strain. Many endoscopists alter their endoscopy practice due to pain or injury, including three of my colleagues who now perform endoscopies while sitting down. Several other colleagues, including technicians in our unit, complain of recurring neck, arm and back pain.

Several factors could improve the ergonomic environment in the endoscopy suite. There is clearly a need for comprehensive guidelines presenting best clinical practice for ergonomics. Training should include information for the endoscopist and the technician on the optimal ergonomics in order to help minimize physical discomfort and maximize productivity. Optimizing the ergonomic environment includes attention to posture and position, procedure room equipment, daily case volumes and endoscope design factors.

We know that performing an endoscopy while maintaining a neutral position of the spine and upper extremities may reduce injury. Neck rotation should be minimized by placing the monitor directly in front of the endoscopist. The monitor height should be just below eye level so that the cervical spine is not in extension. Additionally, the bed level should be adjusted to avoid undue flexion of the lower back. Equipment such as cushioned floor mats can also decrease foot discomfort from prolonged standing. A two-piece lead apron during fluoroscopic procedures will lessen weight placed on the intervertebral disk spaces, as compared to a single full body shield.

There should also be recognition of muscle fatigue and adequate rest time allowed for recovery between procedures.

In general, the design of the endoscopy needs to be retooled to better fit ergonomic principles. The basic shape of the endoscope has not changed over time.

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References

T he hepatitis C virus is primed to develop resistance to direct acting antiviral drugs (DAAs). This stems from several aspects of HCV biology including an extraordinary rate of viral turnover in infected individuals and the error-prone nature of the viral RNA dependent RNA polymerase. Assumptions based on these characteristics led to modeling studies that predicted that every possible single and double mutant virus is created daily in chronically infected individuals. These assertions, combined with data from protease inhibitor monotherapy studies in humans, demonstrated the rapid emergence of viral resistant variants and led to early declarations that resistance to HCV DAAs had the potential to significantly impact clinical treatment responses, particularly in cases of re-treatment of patients who had previously failed DAA containing therapy. These concerns were further supported by Phase 3 data of simeprevir, an NS3 protease inhibitor, plus pegylated interferon and ribavirin, which demonstrated a significant negative impact of baseline resistance (in the form of the Q80K variant) in genotype 1a patients treated with this combination. Based on this data, we saw the first FDA label indicating that alternative therapy should be selected in individuals with the Q80K, effectively ushering in the first era of HCV resistance testing. Resistance testing was “on” sort of.

In practice, simeprevir was rarely used in combination with interferon and ribavirin. Sofosbuvir, a potent nucleotide polymerase inhibitor with an extremely high barrier to resistance, was approved at roughly the same time. Based on the COSMOS data, these two resistance, was approved at roughly the same time, in most cases more than two years.2

The case for baseline resistance testing is best exemplified by treatment with grazoprevir/ elbasvir in patients with genotype 1a HCV. In this case, baseline NS5A resistance testing is the best indicator for choosing the appropriate treatment regimen; 12 weeks without ribavirin in those with no NS5A resistance and 16 weeks plus ribavirin in those with baseline resistance. Indeed, the product label for this regimen, recently approved by FDA, does recommend baseline NS5A resistance testing in genotype 1a patients. Resistance here to stay? It seems unlikely to me.

Is resistance here to stay? It seems unlikely to me. The next step of DAA regimens will not only be truly pangenotypic, but are composed of inhibitors with improved resistance profiles. Combine this with triple-class regimens, which are not far off, and it becomes difficult to envision a large role for HCV resistance testing, even in patients who have previously failed a DAA regimen. A small resistance niche may still exist, not for determining which regimen, but in tailoring treatment duration to the genotype NS5A resistance were significant predictors of response in a multivariable analysis.3 Similarly, in combined data sets with sofosbuvir/ledipasvir treated patients show consistently lower SVR rates in those with baseline NS5A resistance.

If resistance testing is back, when should it be done? Two scenarios make sense for HCV resistance testing currently: 1) after failure of an NS5A-containing DAA regimen and 2) at baseline to guide treatment approaches when using certain regimens in specific populations. Based on limited data, patients failing an NS5A-containing regimen who do not have NS5A resistance may be retreated with a regimen containing an NS5A inhibitor, provided other things are also changed, such as extension of treatment duration or the addition of ribavirin. In contrast, those with NS5A resistance seem most likely to benefit from the addition of DAAs with different mechanisms of action. Finally, combined data sets looking at the impact of baseline NS5A resistant variants clearly show a negative impact of variants on treatment responses.2. Dvory-Sobol, H. Predictors of Response Hepatology 62, 554A-554F (2015).

For example, does treatment duration need to be extended or ribavirin added in select situation with resistance present? However for the vast majority of patients resistance testing will (again) not be needed. Of course, we have underestimated HCV resistance before ... and maybe I am again.2

REFERENCES


HARVONI is now approved for more chronic HCV patient types: HCV/HIV-1 co-infected and GT 4, 5, or 6 patients

HARVONI delivered high cure (SVR) rates in subjects with HCV/HIV-1 co-infection1,a

OVERALL CURE RATE IN GT 1 OR 4 HCV/HIV-1 CO-INFECTED SUBJECTS1,a
ION-4 (N=335)

96%

• HARVONI delivered consistently high cure rates regardless of prior HCV treatment experience or cirrhosis status (94% in subjects with cirrhosis and 98% in treatment-experienced subjects with cirrhosis)1

• The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. See the Drug Interactions section of the HARVONI Prescribing Information for potentially significant drug interactions with HIV antiretrovirals1

• For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed on the next page1

*Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment. Achieving SVR is considered a virologic cure.1

Study Design1
ION-4: an open-label trial that included GT 1 and 4 treatment-naïve and treatment-experienced subjects (N=335) with HCV/HIV-1 co-infection with or without cirrhosis. Subjects received HARVONI for 12 weeks. Treatment-experienced subjects had failed prior treatment with Peg-IFN + RBV, Peg-IFN + RBV + PIs, or sofosbuvir + RBV. None of the 8 GT 4 subjects had cirrhosis. Subjects were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir disoproxil fumarate, administered with efavirenz, rilpivirine, or raltegravir.

INDICATION
HARVONI is indicated for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
• If HARVONI is used in combination with ribavirin (RBV), all contraindications, warnings and precautions, in particular pregnancy avoidance, and adverse reactions to RBV also apply. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS
• Risk of Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Amiodarone is not recommended for use with HARVONI due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.
HARVONI IS THE ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE

1 TABLET ONCE A DAY
WITHOUT IFN or RBV

Recommended treatment duration for HARVONI

<table>
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<th>GT 1</th>
<th>GT 4, 5, 6</th>
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<td>8 weeks</td>
<td>12 weeks</td>
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- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir.
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed above. Refer to the Drug Interactions section of the HARVONI Prescribing Information for dosage recommendations for concomitant HIV-1 antiviral drugs.

HARVONI DELIVERED HIGH CURE (SVR) RATES IN A BROAD RANGE OF GT 1 SUBJECTS

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS (N=1042/1079)

97%

- Overall cure rates were 94%-99% across three HARVONI Phase 3 clinical trials.
- The HARVONI clinical trial program enrolled the most challenging subjects, regardless of GT 1a or 1b subtype, prior experience with HCV therapy, or presence of cirrhosis.

HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS

- Adverse reactions (all grades) reported in ≥5% of GT 1 subjects receiving 8, 12, or 24 weeks of treatment with HARVONI (in ION-3, ION-1, and ION-2): fatigue (13%-18%), headache (1%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%).
- No hematologic monitoring or dose adjustments are required with HARVONI.

MORE THAN 200,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US

HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH

Support Path is a suite of resources that assists with benefits investigations and prior authorizations, and identifies potential financial assistance for patients, such as the HARVONI co-pay coupon program.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS
Most common (≥10%, all grades) adverse reactions were fatigue, headache and asthenia.

DRUG INTERACTIONS
- In addition to rifampin and St. John’s wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytin, rifabutin, and rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.
INDICATIONS AND USAGE: HARVONI is indicated for the treatment of chronic hepatitis C virus (HCV) genotypes (GT) 1, 4, 5, or 6 infection.

CONTRAINdications: HARVONI is contraindicated with ribavirin (RBV), the contraindications to RBV also apply to this combination regimen. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS: Serous Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and asystole requiring pacemaker intervention, have been reported in patients coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients; also take beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect has not been evaluated in patients coadministered with HARVONI. The safety of HARVONI is not recommended for patients taking amiodarone who will be coadministered with HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone’s long half-life patients discontinuing amiodarone just prior to starting HARVONI. Counsel patients about the risk of self-monitoring of their heart rate and cardiovascular monitoring in an in-patient setting for the first 48 hours of coadministration. Amiodarone should be considered among those subjects who coadministered with HARVONI. The most common adverse reactions occurring in at least 10% of subjects were headache (20%) and fatigue (17%).

Common Adverse Reactions Reported in Clinical Trials: less than 5% of subjects receiving HARVONI in any one trial; these events have been included in the above summary of potential serious adverse reactions. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John’s wort) is not recommended. Postmarketing reactions are decreased ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Coadministration is not recommended. Risk of Reduced Therapeutic Effect Due To Use With P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations, and may lead to a reduced HARVONI effect. Coadministration is not recommended. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John’s wort) is not recommended.

Risk Adverse Effects with RBV Combination Treatment: If HARVONI is administered with RBV, the warnings and precautions for RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to RBV prescribing information.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir is not recommended.

ADVERSE REACTIONS: Most common adverse reactions (incidence greater than or equal to 10%, all grades) were fatigue, headache, and asthenia. GT 1 Subjects with Compensated Liver Disease (With and Without Cirrhosis): Adverse reactions were generally similar to placebo in GT 1 subjects treated with HARVONI. Ledipasvir and sofosbuvir were based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-1, ION-3, and ION-2) in subjects who received HARVONI once daily for 12 weeks with or without ribavirin (RBV). The safety profile in these subjects was similar to that observed in subjects with chronic HCV GT 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were headache (18%), asthenia (14%) and fatigue (10%).

GT 1 Treatment-Experienced Subjects with Cirrhosis (SIRIUS): The safety assessment of HARVONI with or without ribavirin (RBV) was based on a randomized, double-blind, placebo-controlled trial. Subjects were randomized to receive HARVONI once daily for 24 weeks without RBV, HARVONI without RBV for 12 weeks and placebo for 12 weeks, or HARVONI with RBV for 24 weeks. Adverse reactions (all grades; majority Grade 1 or 2) observed in at least 5% greater frequency reported in subjects receiving HARVONI for 24 or 24 weeks of HARVONI + RBV for 24 weeks, were: headache (10% or 18%), diarrhea (4% or 7%), and fatigue (8% or 15%). Most common adverse reactions occurring in at least 10% of subjects were headache (20%) and fatigue (17%).

Ledipasvir solubility decreases as pH increases. With amiodarone this leads to a reduced ledipasvir concentration. Harvoni HCV treatment is not recommended in patients on amiodarone. Amiodarone: Non-Cardiovascular: There have been reports of serious liver injury, including liver failure and liver cancer in patients who started amiodarone, who have no other alternative, viable treatment options, and due to amiodarone’s long half-life patients discontinuing amiodarone just prior to starting HARVONI. Counsel patients about the risk of self-monitoring of their heart rate and cardiovascular monitoring in an in-patient setting for the first 48 hours of coadministration. Amiodarone should be considered along with the mother’s clinical need for HARVONI and any potential adverse effects on the breastfed infant and/or from the underlying maternal condition. If HARVONI is administered with RBV, the lactation recommendation is the same as for this combination regimen. Refer to RBV prescribing information.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical experience with HARVONI included 225 subjects aged 65 and over (39% of total number of subjects in the clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, age can affect the selection of a starting dose in elderly patients but this is not applicable to HARVONI effect. Coadministration is not recommended.

Hepatic Impairment: No dosage adjustment of HARVONI is recommended for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 ml/min/1.73m2) or end stage renal disease (ESRD) requiring dialysis or peritoneal dialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 ml/min/1.73m2) or end stage renal disease (ESRD) requiring dialysis or peritoneal dialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

USE IN SPECIFIC POPULATIONS:

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Consider the potential for HARVONI to cause fetal harm when prescribing to a pregnant woman. If HARVONI is administered with RBV, the combination regimen is contraindicated in pregnant women and man in which female partners are pregnant. Refer to the RBV prescribing information.

Lactation: It is not known if HARVONI and its metabolites are excreted in breast milk. Studies in rats have demonstrated that ledipasvir and GS-33107 are secreted in milk without effect on nursing pups. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for HARVONI and any potential adverse effects on the breastfed infant and/or from the underlying maternal condition. If HARVONI is administered with RBV, the lactation recommendation is the same as for this combination regimen. Refer to the RBV prescribing information.

September 2015, 52 gastroenterologists from 24 states met on Capitol Hill. Our goal was two-fold — to brief members of the U.S. Congress and their staffers about the potentially regressive effects of the proposed Centers of Medicare and Medicaid Services (CMS) cuts to colonoscopy reimbursements, and also to advocate for increases to NIH research funding.

As a member of the AGA Government Affairs Committee and AGA Trainee and Young GI Committee, I was given the opportunity to participate in this annual event, better known as AGA Advocacy Day. The event welcomes AGA members from all over the country to Washington, D.C. to raise awareness among government officials about the policy issues most critical to clinicians and researchers in gastroenterology.

Between our respective AGA committee meetings, we shuttled ourselves to the Hill, each with an itinerary of three to six appointments with Representatives, Senators and staffers. We traversed the long hallways of the historic Longworth, Hart, Cannon and Rayburn congressional buildings to deliver five-minute pitches about the issues that matter most to the GI community.

The culmination of this interaction was our specific “ask”— for our representative to sign a “Dear Colleague” letter to CMS expressing concern for the then-proposed colonoscopy reimbursement cuts, and requesting CMS to consider the impact of such policy on colorectal cancer (CRC) screening. Some of us were greeted with smiles and words of encouragement from congressional representatives while other encounters, despite our enthusiasm, left us a bit discouraged.

Upon arrival in Washington, D.C. in September, I knew very little about what Advocacy Day would entail. I suddenly found myself in a slight panic sitting at the Advocacy Day breakfast, listening to a briefing on what to expect on the Hill and how to handle new and potentially difficult interactions. Looking around the room, I wondered if, at two months into my first GI faculty position, I would be the best candidate to represent AGA in front of the likes of Sens. Dianne Feinstein and Barbara Boxer, who represent my home state of California in Congress.

There was little time to coddle this anxiety though. Following brief instructions and talking points, our team of California AGA members headed to our first of six scheduled meetings on the Hill. Fortunate to have a few seasoned lobbyists on my team, I learned quickly, embracing the “see one, do one ...” mantra we often champion in medicine.

After silently participating in our first meeting at Rep. Raul Ruiz’s office, I took the lead in our appointment with Rep. Jackie Speier — a woman whose historic reverence and political longevity only added to my nervousness. I shared my personal journey as a young researcher studying barriers to CRC screening in the Veterans Affairs Healthcare Network. I emphasized that, while this cancer is largely preventable, only 62 percent of Americans undergo screening. And that among Black, Hispanic and Asian racial/ethnic minorities, screening rates are even lower. I added that limiting access to colonoscopy for Medicare beneficiaries is contrary to the National Colorectal Cancer Roundtable goal to screen 80 percent of Americans by 2018.

Along with the other AGA members in my group, I also asked members of Congress to protect NIH against additional funding cuts that limit our ability to conduct essential scientific research. NIH dollars for science decreased by over 22 percent between 2003 and 2013, and the number of RO1-equivalent investigator grants fell by 24 percent. More and more, young clinician-scientists are faced with the difficult decision to remain in academic research in the setting of seemingly impossible funding.

As the morning continued, my panic about being a suitable envoy for our gastroenterologist community rapidly receded. It became clear to me that the policy issues in question were critically relevant to my career. In order to sustain our field, we must defend the value of our life-saving procedures like colonoscopies and assure that there is continued funding to research the delivery, technology and treatments for the diseases we treat.

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Hugh F. Culverhouse Chair for Esophageal Disorders
Director, Division of Digestive Diseases & Nutrition; Director, Joy McCann Culverhouse Center for Esophageal and Swallowing Disorders
University of South Florida Morsani College of Medicine, Tampa, FL
39. Culverhouse was an accomplishedreur.

Newer Endoscopic Therapies for GERD

For the last 55 years, anti-reflux surgery (Nissen or Toupet fundoplication) has had excellent outcomes, few side effects and commendable durability for a functional repair. The procedure is a true anti-reflux operation, increasing lower esophageal sphincter pressure and eliminating acid reflux in 90% of patients. Thirty-day mortality is less than 1% and (0% to 1% in many centers), perioperative morbidity usually due to co-morbid illnesses, and the durability measured by revisional surgery is less than 1% over more than 15 years of follow-up.1 Yes, “heartburn” returns in many patients and some require PPIs, but only a fraction have abnormal pH tests and most are back on PPIs for non-specific dyspeptic symptoms.

Why then is there an interest in alternative endoscopic and surgical treatments for GERD? I believe because of the potential financial gains and the misrepresentation of expected post-operative complications after fundoplication, including dysphagia, gas-bloat syndrome and diarrhea. Some dysphagia occurs in everyone, occasionally requiring esophageal dilation and is a troubling problem in fewer than 5 percent of patients after one year. The best predictors of post-operative dysphagia are dysphagia before surgery and the same can be said about gas-bloat syndrome. Over the last 30 years, my experience at four academic centers with four surgeons finds these side effects are minimal by proper patient selection. My “golden rules” are:

1. Esophageal manometry in all and testing off PPIs for non-specific dyspeptic symptoms.

2. Do not allow an abnormal pH test to be the sole criteria for surgery, especially in anxious patients — all the “pieces of the puzzle” should fit together.

3. Avoid the “intractable patient,” especially with anxiety/depression or irritable bowel driving their complaints.

Therefore, new alternative treatments must be measured against the “gold standard” of fundoplication with respect to symptoms and pH control, safety and durability. Let’s see who are the “pretenders” for the royal kingdom of the Nissen fundoplication.

The first is the Stretta procedure (Mederi Therapeutics), first approved by FDA in 2000, which reappeared again in 2005 after bankruptcy and at least four procedure-related deaths. The device uses radiofrequency ablation to decrease lower esophageal sphincter (LES) compliance and reduce transient LES relaxation, but some neurolysis also contributes to symptom improvement. Advocates, including SAGES, boast about the more than 15,000 patients treated with this device and over 80 publications, all uncontrolled observational meta-analyses.2 The U.S. study found good control of regurgitation superior to sham and PPIs, but 15% failed endoscopic treatment in the first six months going back on PPIs. The European experience was similar at six months, with excellent heartburn and pH control, similar to PPIs, but at one year less than 30% had acid pH normalization and 60% were back on PPIs.3 Here again complications are not rare. The database maintained by the FDA reported over 40 complications with TIF of which 35 percent were esophageal perforations often requiring hospitalization and sometimes surgical repair.4 So again, despite the enthusiasm, how do I “sell” this operation to a patient with lifelong GERD generally better on inexpensive PPIs, when the durability at one year is poor, with most back on PPIs? Maybe the surgeon can offer a “money-back guarantee” to the customer if unhappy with the results.

I do want to clarify that this esophagologist is not against all new surgical innovations. I have enthusiasm for the magnetic sphincter augmentation device (LINX, Thorax Medical) because it normalizes acid reflux in most patients, complications are few and reversible, and most importantly the operation is durable for up to five years.5 Unfortunately, insurance companies are reluctant to pay for this procedure. Until reimbursement changes, this esophageal expert wants to offer my patients only the best — and that’s a Nissen fundoplication by an experienced surgeon after careful esophageal testing.

Did you know?
The AGA STAR Registry, developed by the AGA Center for GI Innovation, is currently working to track real-world data on the TIF procedure to guide future care decisions.
established in 2014, the AGA Center for Diagnostics and Therapeutics joins the AGA Center for GI Innovation and Technology and the AGA Center for Microbiome Research and Education as the third center of the AGA Institute. The center’s mission statement, which was recently approved by the AGA Institute Governing Board, is “to support the development of therapies and diagnostic tests that will enhance human health and improve the lives of patients with digestive disorders.”

The Center for Diagnostics and Therapeutics operates under the guidance of its own scientific advisory board, the current members of which are listed in the table. The board has broad representation from academia, private practice, the pharmaceutical industry and FDA. Rajeev Jain, MD, AGAF, currently acts as our liaison with the AGA Institute Governing Board. Broadly stated, the objective of the center is to “provide objective, independent guidance and facilitate relationships to the pharmaceutical, biotech, and diagnostics industries, policy makers, regulatory bodies, investors, and clinicians on the development of therapies and diagnostic tests.” Clearly, that is quite a broad remit, which is why we have such a diverse scientific advisory board.

What has the center achieved so far?

The center’s scientific advisory board met formally on three occasions in 2015 to help identify its precise role and to prioritize our efforts. Since the active participation of FDA is so critical to achieving our objectives, AGA Institute President Michael Camilleri, MD, AGAF, and I met with FDA personnel at their facility in June 2015.

We have since established a set of issues on which we might collaborate, and have identified areas where the center may provide guidance to FDA on relevant matters. Our first such contribution was a detailed and comprehensive response to FDA’s draft guidance for industry titled “Gastroprosthetic Clinical Evaluation of Drugs for Treatment.” Debra G. Silber, MD, PhD, and Scott Harris, MD, AGAF, of the scientific advisory board, provided extensive input to that document from the perspectives of the pharmaceutical industry and clinical investigators.

The first symposium held under the auspices of the Center for Diagnostics and Therapeutics concerned the issue of local versus central reading of endoscopic images in inflammatory bowel disease (IBD). This has implications for the design and interpretation of clinical trials of new agents in IBD and, potentially, for the routine clinical care of IBD patients. This symposium was held in Washington, D.C., on Oct. 2, 2015, and was attended by 57 audience members, including practicing gastroenterologists involved in clinical trials, personnel from the pharmaceutical industry and FDA employees. William Sandborn, MD, AGAF, had initially suggested this topic and helped devise the program. The center aims to publish the deliberations and conclusions from the conference in Clinical Gastroenterology and Hepatology as a whitepaper.

Future plans for the center

In 2016, there will be a Center for Diagnostics and Therapeutics-sponsored symposium at Digestive Disease Week® regarding the drug development process from the perspectives of a clinical investigator, a trial sponsor and FDA. We also plan to hold the first of a series of annual Drug Discovery Conferences. The 2016 conference, which Nimish Vakil, MD, AGAF, and I will co-chair, will focus on upper GI tract disorders. The program is currently being finalized. The conference will address unmet needs and potential therapeutic advances in GERD, esophageal eosinophilia, functional dyspepsia and gastroparesis.

We also see ourselves as taking an “honest broker” role in liaison between industry and FDA whenever appropriate.
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CALIFORNIA

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Work Schedule:
• One in 10 weekend call; One in 12 night call
• Competitive compensation and benefit package
• Hours M-F between 8am-5pm; full-time opportunity
• Quality ERCP experience is desired but not mandatory
• Established 19-physician-member GI group to grow into 21 members by August of 2016.
• Two-year partnership track
• Four endoscopy centers plus other anciliaries
• Quality ERCP experience is desired but not mandatory
• Hours M-F between 8am-5pm; full-time opportunity available
• Competitive compensation and benefit package
• One in 10 weekend call; One in 12 night call

NORTH CAROLINA

Gastroenterologist
• Established 19-physician member GI group to grow into 21 members by August of 2016.
• Two-year partnership track
• Four endoscopy centers plus other anciliaries
• Quality ERCP experience is desired but not mandatory
• Hours M-F between 8am-5pm; full-time opportunity available
• Competitive compensation and benefit package
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VA Sierra Nevada Health Care System, Reno, NV is accepting applications for U.S. citizen gastroenterologists, BC/BE preferred. VASNHCS provides an excellent patient care environment with learning, teaching, and research opportunities, a state of the art endoscopy lab, and an advanced electronic medical records reporting system. Provide a variety of therapeutic and diagnostic GI procedures, including ERCP. Share knowledge and clinical expertise with academic affiliates, professional staff, and support personnel in our interdisciplinary approach to patient-centered care delivery.

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