

Review

Unmet needs in the post-direct-acting antivirals era: The risk and molecular mechanisms of hepatocellular carcinoma after hepatitis C virus eradication

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Hepatitis C virus (HCV) infection is one of the major etiologies of hepatocellular carcinoma (HCC) with approximately 30% of HCC being due to HCV infection worldwide. HCV eradication by antivirals greatly reduces the risk of HCC; nevertheless, HCC remains to occur in chronic hepatitis C (CHC) patients who have achieved a sustained virological response (SVR). The proportion of post-SVR HCC among newly diagnosed HCC patients is increasing in the direct-acting antiviral (DAA) era and might be due to preexisting inflammatory and fibrotic liver backgrounds, immune dysregulation between host and virus interactions, as well as host epigenetic scars, genetic predispositions and alternations. By means of applying surrogate markers and adopting risk stratification, HCC surveillance should be consistently performed in high-risk populations. In this review, we discuss the possible molecular mechanism, risk factors, and HCC surveillance strategy for HCC development after HCV eradication in CHC patients. ([Clin Mol Hepatol 2024;30:326-344](#))

Keywords: HCV; HCC; SVR; Genetic; Epigenetic; Surveillance

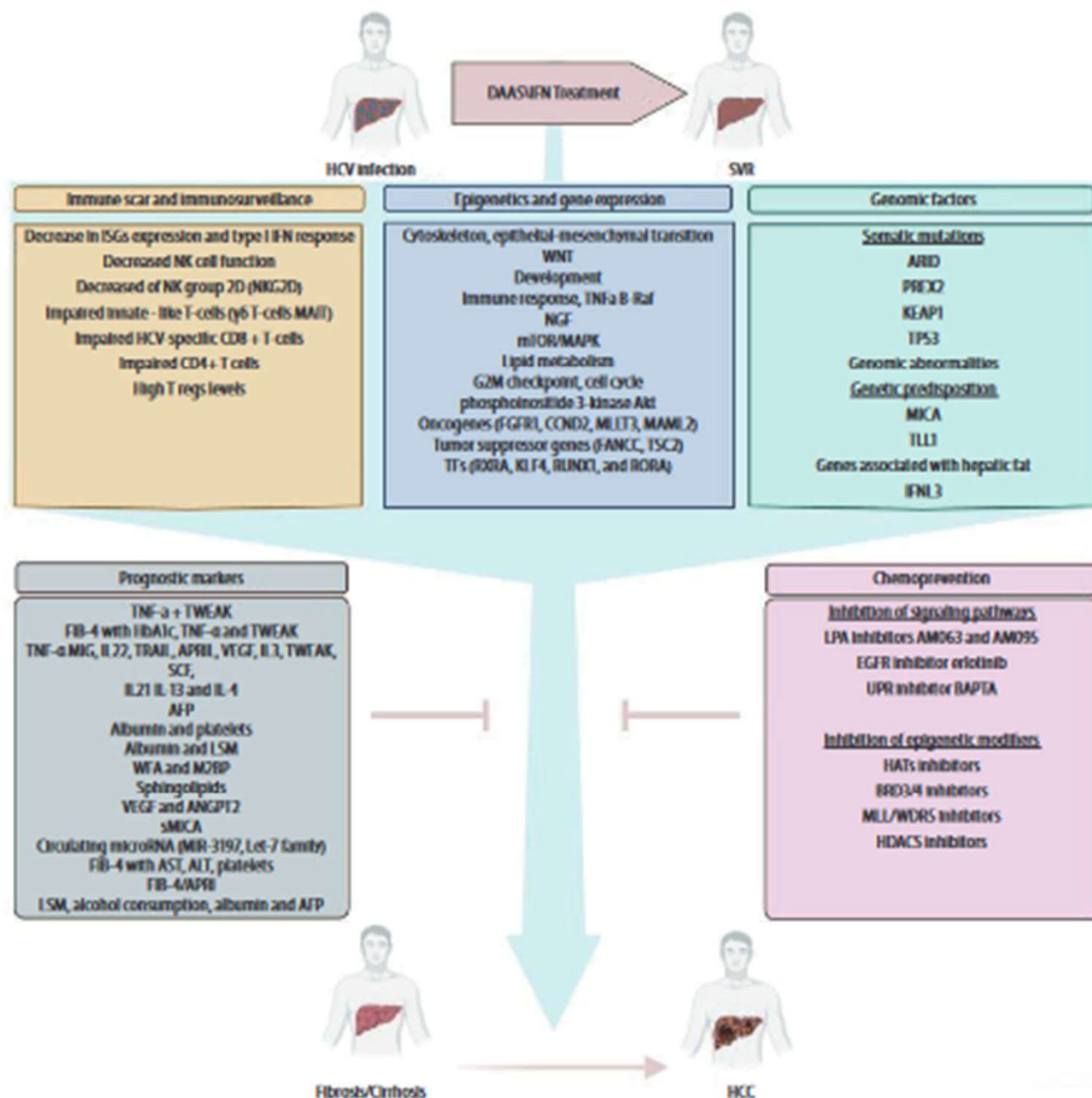


Figure 1. Scheme of molecular mechanisms of hepatocellular carcinoma after HCV eradication. Development of HCC pre- and post-SVR is related to impaired immune response and immune surveillance, epigenetic and gene expression alterations and genomic factors. Identified persistent mechanisms that remain impaired after HCV SVR and prognostic markers for HCC risk post SVR and HCC chemoprevention targets are shown. HCV, hepatitis C virus; SVR, sustained virological response; HCC, hepatocellular carcinoma; DAA, directly acting antiviral; IFN, Interferon.

Table 4. Unmet needs for the post-SVR HCC

- Identify the target population for surveillance on the cost-effective basis
- Define the screen interval and duration after achieving SVR
- Adopt precise screening tools including image modalities and biomarkers
- Marginal benefit of HCC risk reduction in patients with decompensated liver cirrhosis
- Predict the high-risk population based on the pathophysiological mechanisms
- Construct a precision medicine-guided strategy that incorporates clinical and molecular surrogates

SVR, sustained virological response; HCC, hepatocellular carcinoma.

dence interval 0.52, 1.00; $P=0.05$) in DAA treated decompensated patients compared to untreated control.¹²⁹

In conclusion, post-SVR HCC remains as occurring in a subset of CHC patients due to preexisting inflammatory and fibrotic liver background, immune dysregulation as well as host epigenetic scar, genetic predispositions and alterations (Fig. 1). There are remaining unmet needs in post-SVR HCC surveillance and management (Table 4). By means of applying surrogate markers and adopting risk stratification, HCC surveillance should be consistently performed in high-risk populations.

Authors' contributions

Conception and design: Ming-Lung Yu. Manuscript draft-

Study suggests an MRI may help doctors predict more aggressive prostate cancer in patients

Findings could indicate which patients need immediate treatment and who can be monitored

Newswise — SOUTHFIELD, MI, Aug. 7, 2024 - New Corewell Health™ research suggests an MRI scan can help predict whether patients with intermediate-risk prostate cancer (cancer confined to the entire prostate) may have more aggressive cancer in five years. Knowing this could potentially help doctors determine if treatment is needed up front vs. using a method called active surveillance where the disease is closely monitored over time. [The study](#), recently published in the Journal of Urology, is the first to evaluate this risk group.

Currently, there has been a growing trend to manage low-risk prostate cancer patients with active surveillance to help patients avoid side effects associated with surgery or radiation. Patients are considered low risk when less than half of one lobe of the prostate is affected, and the cancer cells haven't mutated or changed much. However, for intermediate-risk patients, choosing what treatment path is best can be a bit more challenging for doctors.

"While active surveillance is the standard of care for low-risk patients, it's been unclear whether patients with a slower-growing form of intermediate-risk prostate cancer should be carefully watched or undergo immediate treatment," said Kiran Nandalur, M.D., principal investigator of the study and a radiologist at Corewell Health William Beaumont University Hospital. "Our data suggests that an MRI can show suspicious lesions based on size and markers of tumor aggression, which may help doctors differentiate a treatment path for these patients."

In the study, about 1,500 low- and intermediate-risk patients across Michigan were examined to determine if individuals with suspicious findings on an MRI test returned with a more advanced stage of the disease within five years. Here's what the study found:

- Overall, 36% of the study participants who were watching their prostate cancer demonstrated more aggressive disease within five years.

- Considering traditional risk factors and using an MRI classification system that rates lesion suspicion, patients with high-risk imaging features were approximately 130% more likely to have more aggressive disease on follow-up than those with low-risk imaging results.
- Suspicious lesions on an MRI indicated more than twice the risk of progressive disease in both low-risk and intermediate-risk prostate cancer patients, which has not been previously shown in the intermediate-risk patients.

"The implication for patients and doctors is that an upfront MRI is important before undertaking any active surveillance for prostate cancer since it may help predict if an individual might come back with worse disease later," Dr. Nandalur said. "This type of imaging helps pave the way for treatment planning so patients can live their lives to the fullest whether they decide to watch their cancer or seek treatment."

Additional institutions contributing to the study include the Department of Urology at Wayne State University in Detroit, Michigan; Michigan Institute of Urology in West Bloomfield, Michigan; Brady Urologic Institute at Johns Hopkins University in Baltimore, Maryland; and the Michigan Urological Surgery Improvement Collaborative.

About Corewell Health™

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The Road Ahead for Engineered T Cells

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Adoptive cellular therapy using chimeric antigen receptors (CARs) has transformed immunotherapy by engineering T cells to target specific antigens on tumor cells. As the field continues to advance, pathology laboratories will play increasingly essential roles in the complicated multi-step process of CAR T-cell therapy. These include detection of targetable tumor antigens by flow cytometry or immunohistochemistry at the time of disease diagnosis and the isolation and infusion of CAR T cells. Additional roles include: i) detecting antigen loss or heterogeneity that renders resistance to CAR T cells as well as identifying alternative targetable antigens on tumor cells, ii) monitoring the phenotype, persistence, and tumor infiltration properties of CAR T cells and the tumor microenvironment for factors that predict CAR T-cell therapy success, and iii) evaluating side effects and biomarkers of CAR T-cell cytotoxicity such as cytokine release syndrome. This review highlights existing technologies that are applicable to monitoring CAR T-cell persistence, target antigen identification, and loss. Also discussed are emerging technologies that address new challenges such as how to put a brake on CAR T cells. Although pathology laboratories have already provided companion diagnostic tests important in immunotherapy (eg, programmed death-ligand 1, microsatellite instability, and human epidermal growth factor receptor 2 testing), it draws attention to the exciting new translational research opportunities in adoptive cellular therapy. (*Am J Pathol* 2024, 194: 1409–1423; <https://doi.org/10.1016/j.ajpath.2024.04.002>)

2024 Gairdner Award recipients paved way for revolutions in cancer treatment, genomics, and global health

FDA-approved CAR T-cell Therapies

Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy that uses a patient's own genetically modified T cells to find and kill cancer. UPMC Hillman Cancer Center was among the first in the nation to offer the FDA-approved CAR T-cell therapies listed below and is western Pennsylvania's most experienced provider, having treated more than 100 patients with CAR T cells.

Our therapies include:

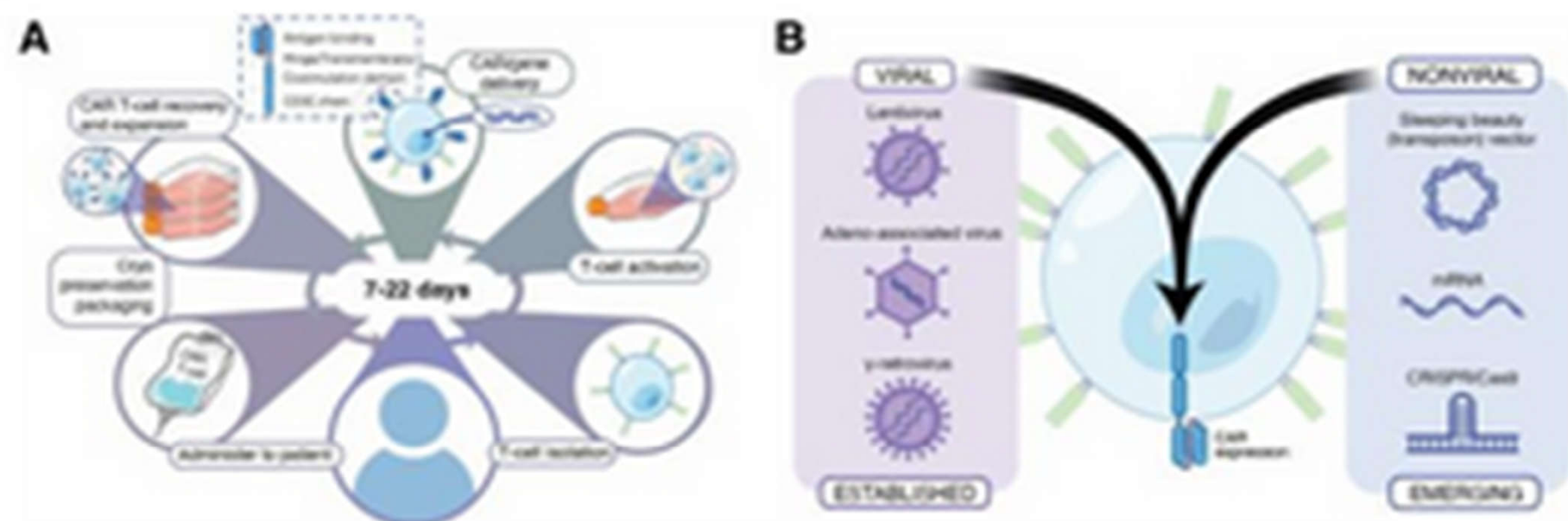



Figure 1 Manufacturing process of chimeric antigen receptor (CAR) T cells. **A** For the production of autologous T cells, it takes 1 to 2 weeks to isolate the T cells, activate them, deliver the CAR, expand the cells, return them from a central facility, and administer them to the patient. **B** Methods to deliver genetic material and express CARs with T cells include viral transduction and nonviral transfections of transposon vectors, mRNA, or CRISPR/Cas9 ribonucleoproteins. Of these, currently US Food and Drug Administration–approved CAR T cells are produced by lentivirus or retrovirus.

Ultrasound detects more cancers in high-risk women with dense breasts

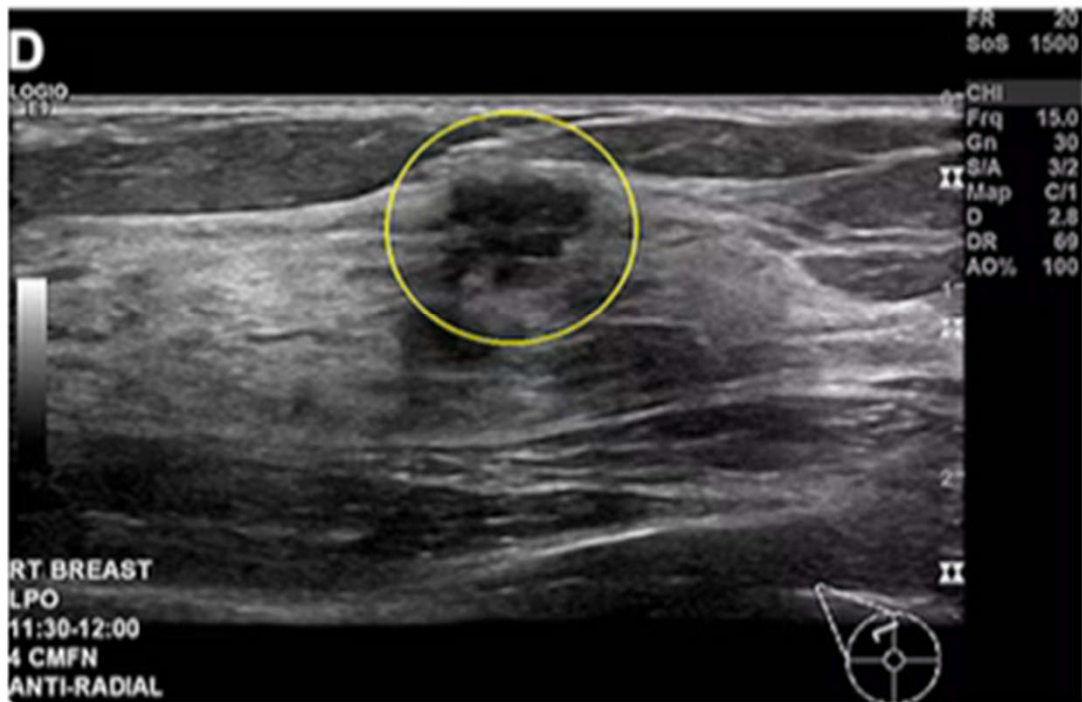
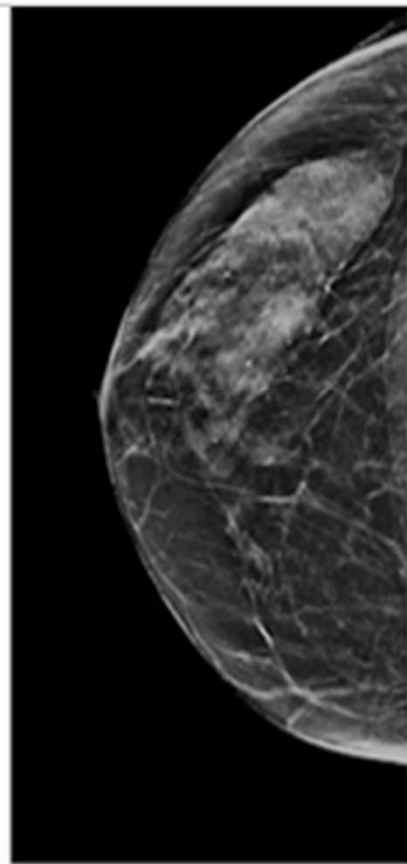
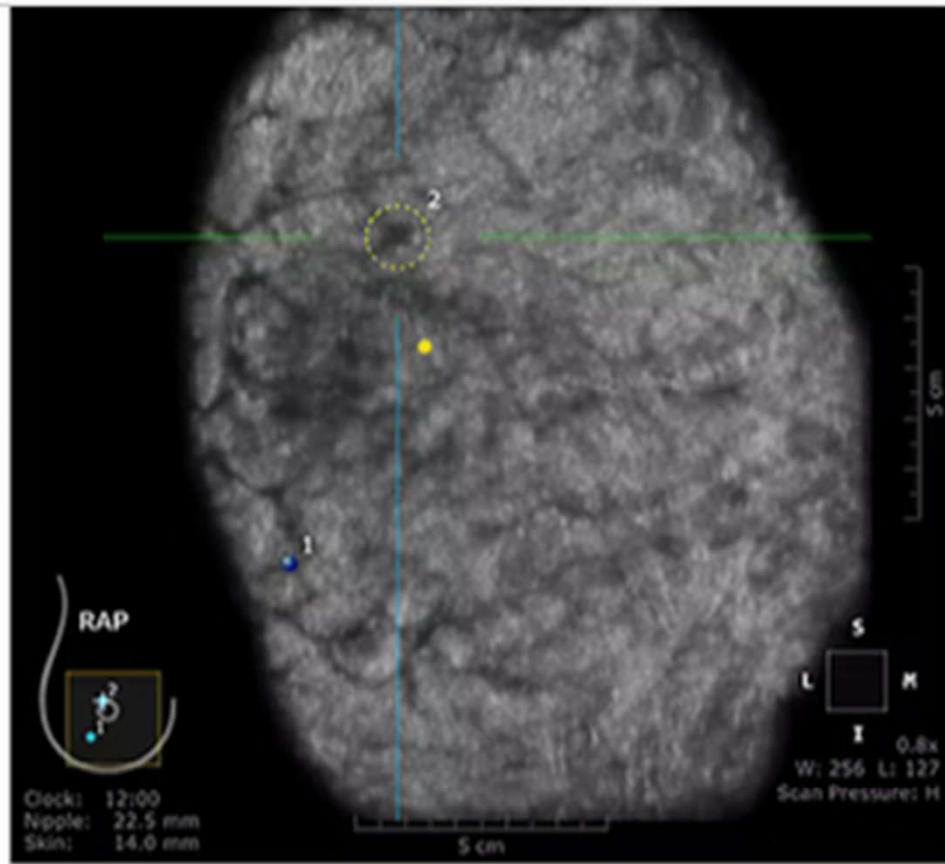
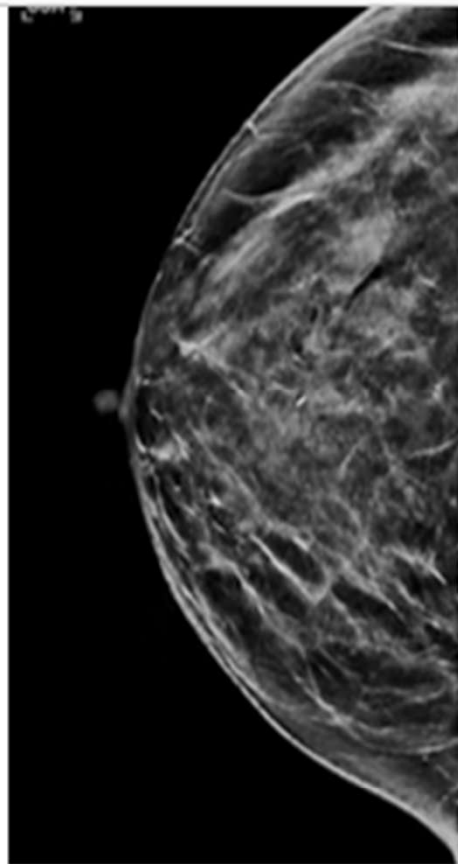
Amerigo Allegretto

Aug 6, 2024



Supplemental breast ultrasound may have utility in imaging women with dense breasts and high risk of advanced or invasive breast cancer, a study published August 6 in *Radiology* found.

Researchers led by Brian Sprague, PhD, from the University of Vermont in Burlington found that women at elevated risk of invasive or advanced breast cancer according to established risk prediction models had high supplemental cancer detection rates on ultrasound screening after a negative mammogram, with a moderate positive predictive value of biopsy.



Sprague also told *AuntMinnie.com* that the team is evaluating the potential population-level impact of risk-based supplemental ultrasound screening strategies by using computer simulation models. The models aim to translate these observed short-term screening outcomes into estimates of long-term outcomes, including breast cancer deaths averted and cumulative false-positive exams.

“The results will inform policymakers and healthcare providers as they consider supplemental screening recommendations,” Sprague said.

Risk stratification is important and can improve ultrasound screening outcomes such as those in the study by Sprague et al, according to an accompanying editorial written by Thomas Helbich, MD, and Panagiotis Kapetas, MD, PhD, from the Medical University of Vienna in Austria.

The editorial authors however added that moving from the current age-driven screening approach to a risk-stratified breast cancer screening approach is “not likely to occur at once.” They wrote that it is also important to identify which imaging methods will best serve different patient subgroups.

Original research

Positioning intestinal ultrasound in a UK tertiary centre: significant estimated clinical role and cost savings

Journal of Clinical Ultrasound and Endoscopy 2014; 12(1): 1-10

performed instead was calculated.

Results 73 of 260 LGIEs (28.1%) and 58 of 105 MREs (55.2%) met the criteria for IUS suitability. Among potential IUS-suitable endoscopy patients, one case each of a <5 mm adenoma and sessile serrated lesion were found; no other significant pathology that would be expected to be missed with IUS was encountered. Among IUS-suitable MRE patients, no cases of isolated upper gastrointestinal inflammation likely to be missed by IUS were found, and extraintestinal findings not expected to be seen on IUS were of limited clinical significance. The predicted cost saving over 1 month if IUS was used instead was £8642, £25 866 and £5437 for MRE, colonoscopy and flexible sigmoidoscopy patients, respectively.

Conclusion There is a significant role for IUS, with annual projected cost savings of up to almost £500 000 at our centre. Non-inflammatory or non-gastrointestinal pathology predicted to be missed in this cohort was of limited clinical significance.

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