Molecular signatures of long-term hepatocellular carcinoma risk in nonalcoholic fatty liver disease

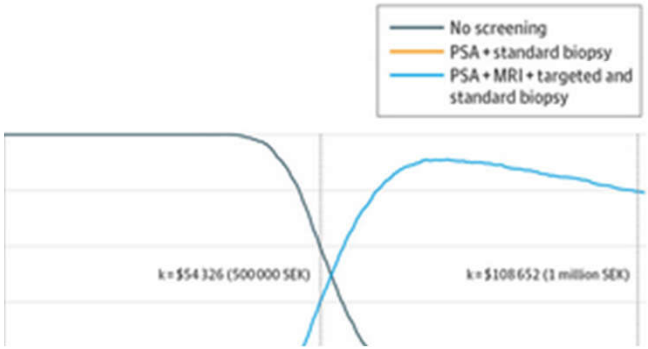
Prediction of hepatocellular carcinoma (HCC) risk is an urgent unmet need in patients with nonalcoholic fatty liver disease (NAFLD). In cohorts of 409 patients with NAFLD from multiple global regions, we defined and validated hepatic transcriptome and serum secretome signatures predictive of long-term HCC risk in patients with NAFLD. A 133-gene signature, prognostic liver signature (PLS)–NAFLD, predicted incident HCC over up to 15 years of longitudinal observation. High-risk PLS-NAFLD was associated with IDO1^{+} dendritic cells and dysfunctional CD8^{+} T cells in fibrotic portal tracts along with impaired metabolic regulators. PLS-NAFLD was validated in independent cohorts of patients with NAFLD who were HCC naïve (HCC incidence rates at 15 years were 22.7 and 0% in high- and low-risk patients, respectively) or HCC experienced (de novo HCC recurrence rates at 5 years were 71.8 and 42.9% in high- and low-risk patients, respectively). PLS-NAFLD was bioinformatically translated into a four-protein secretome signature, PLSec-NAFLD, which was validated in an independent cohort of HCC-naïve patients with NAFLD and cirrhosis (HCC incidence rates at 15 years were 37.6 and 0% in high- and low-risk patients, respectively). Combination of PLSec-NAFLD with our previously defined etiology-agnostic PLSec-AFP yielded improved HCC risk stratification. PLS-NAFLD was modified by bariatric surgery, lipophilic statin, and IDO1 inhibitor, suggesting that the signature can be used for drug discovery and as a surrogate end point in HCC chemoprevention clinical trials. Collectively, PLS/PLSec-NAFLD may enable NAFLD-specific HCC risk prediction and facilitate clinical translation of NAFLD-directed HCC chemoprevention.

MRI after PSA testing is more cost-effective than standard protocol

By Kate Madden Yee, AuntMinnie.com staff writer

November 10, 2022 -- Prostate cancer screening that combines prostate-specific antigen (PSA) testing followed by an MRI is more cost-effective than the traditional pathway of PSA to standard biopsy, according to a study published November 10 in *JAMA Oncology*.

The findings also suggest that a strategy of PSA testing, MRI, and then biopsy if needed could reduce unnecessary biopsies, wrote a team led by Shuang Hao of the Karolinska Institute in Stockholm, Sweden.



Cost-effectiveness of Prostate Cancer Screening Using Magnetic Resonance Imaging or Standard Biopsy

Shuang Hao, MSc, MPH; Andrea Discacciati, PhD; Martin Eklund, PhD; et al

Original Investigation | November 10, 2022

Cost and QALY comparison between three MRI prostate cancer screening strategies			
Strategy	**Costs (in millions) per 100,000 men**	**Quality-adjusted life years (QALY)**	**Incremental cost-effectiveness ratio (ICER) per QALY**
No screening	$212	1,463,945	N/A
PSA and MRI with both targeted and standard biopsies	$252.3	1,464,696	53,736
PSA and standard biopsy	$271.2	1,464,801	69,254

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

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JOURNAL ARTICLE

Management of Hyperglycemia in Hospitalized Adult Patients in Non-Critical Care Settings: An Endocrine Society Clinical Practice Guideline FREE

Mary T Korytkowski, Ranganath Muniyappa, Kellie Antinori-Lent, Amy C Donihi, Andjela T Drincic, Irl B Hirsch, Anton Luger, Marie E McDonnell, M Hassan Murad, Craig Nielsen ... Show more

The Journal of Clinical Endocrinology & Metabolism, Volume 107, Issue 8, August 2022, Pages 2101–2128,
https://doi.org/10.1210/clinem/dgac278

Recommendation 1.1

In adults with insulin-treated diabetes hospitalized for noncritical illness who are at high risk of hypoglycemia, we suggest the use of real-time continuous glucose monitoring (CGM) with confirmatory bedside point-of-care blood glucose (POC-BG) monitoring for adjustments in insulin dosing rather than point-of-care blood glucose (POC-BG) testing alone in hospital settings where resources and training are available. (2⊕⊕◯◯)

Remarks

- In hospitals where CGM is not available, monitoring of blood glucose (BG) levels can be continued with POC-BG testing as an alternative option.

- Patients identified as being at high risk for hypoglycemia include but are not limited to the following criteria: age ≥ 65 years; body mass index ≤ 27 kg/m^2; total daily dose of insulin ≥ 0.6 units/kg; history of stage ≥3 chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2), liver failure, cerebrovascular accident, active malignancy, pancreatic disorders, congestive heart failure, or infection; history of preadmission hypoglycemia or hypoglycemia occurring during a recent or current hospitalization; or impaired awareness of hypoglycemia.

- This recommendation does not apply to situations in which CGM may not be accurate, including in patients with extensive skin infections, hypoperfusion, or hypovolemia or those receiving vasoactive or pressor therapy. In addition, some

Recommendation 2.1

In adult patients who are hospitalized for noncritical illness and experience hyperglycemia while receiving glucocorticoids (GCs), we suggest glycemic management with either neutral protamine Hagedorn (NPH)-based insulin or basal bolus insulin (BBI) regimens. (2⊕⊕◯◯)

Remarks

- An NPH-based regimen may consist of NPH (with or without prandial insulin) given in divided doses depending on the timing, pharmacokinetics, and frequency of the specific GC being administered. NPH insulin may be added to BBI if the patient is already on this regimen.

- Management of patients with GC-associated hyperglycemia requires ongoing BG monitoring with adjustment of insulin dosing. All therapies require safeguards to avoid hypoglycemia when doses of GCs are tapered or abruptly discontinued.

Question 3. Should continuous subcutaneous insulin infusion pump therapy be continued vs transitioning to scheduled subcutaneous insulin therapy for adults with diabetes on pump therapy who are hospitalized for noncritical illness?

Recommendation 3.1

In adult patients using insulin pump therapy for diabetes management prior to admission for noncritical illness, we suggest that these patients continue insulin pump therapy rather than changing to subcutaneous (SC) basal bolus insulin (BBI) therapy in hospitals with access to personnel with expertise in insulin pump therapy. Where expertise is not accessible, we suggest that patients with anticipated hospital length of stay (LOS) of more than 1 to 2 days be transitioned to scheduled subcutaneous (SC) basal bolus insulin (BBI) before discontinuation of an insulin pump. (2⊕⊕◯◯)

Remarks

- Patients with an impaired level of consciousness, inability to appropriately adjust pump settings, critical illness (intensive care unit care), diabetic ketoacidosis, or hyperosmolar hyperglycemic state are not candidates for inpatient use of the insulin pump. Any change in a patient's condition that would interfere with their ability to safely self-manage the insulin pump device requires removal and transition to SC therapy (Table 3). Availability of supplies (provided by the patient or patient's family) over the course of the hospitalization is necessary. Adaptation of the basal rate may be needed at time of admission.

- Patients using hybrid closed-loop insulin pump therapy may be able to continue this at time of admission if they meet

Recommendation 4.1

In adult patients with diabetes who are hospitalized for noncritical illness, we suggest providing inpatient diabetes education as part of a comprehensive diabetes discharge-planning process, rather than not providing inpatient diabetes education. (2⊕⊕⊕◯)

Remarks

- Inpatient diabetes education is best provided by diabetes care and education specialists (DCES). Where availability of DCES is limited, DCES can serve as a resource to healthcare providers specifically tasked to provide inpatient diabetes education (eg, staff nurses, pharmacists, dieticians, etc.) by providing training and support.

- Ideally, the DCES should be Certified Diabetes Care and Education Specialists and/or hold the Board Certified-Advanced Diabetes Management credentials or be working toward 1 of these certifications.

- A comprehensive diabetes discharge-planning process includes education on and validation of diabetes survival skills, referral for outpatient diabetes self-management education and support, scheduling diabetes care follow-up appointments, and ensuring access to the medications and supplies required for diabetes self-management following discharge.

- In the case of limited personnel, healthcare providers providing diabetes education could prioritize education for patients at

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DNA methylation fingerprint for the diagnosis and monitoring of hepatocellular carcinoma from tissue and liquid biopsies

Emanuel Gonçalves, Maria Reis, José B Pereira-Leal, Joana Cardoso[#]

Results

Our machine learning pipeline identified differentially methylated regions in HCC, some associated with transcriptional repression of genes related with cancer progression, that benchmarked positively against independent methylation signatures. Combining our signature of 38 DNA methylation regions, we derived a HCC detection score which confirmed the utility of our approach by identifying in an independent dataset 96% of HCC tissue samples with a precision of 98%, and most importantly successfully separated cfDNA of tumour samples from healthy controls. Notably, our risk score could identify cell-free DNA samples from patients with other tumours, including colorectal cancer.

Conclusions

Taken together, we propose a comprehensive HCC DNA methylation fingerprint and an associated risk score for the early diagnosis and early relapse detection of HCC from liquid biopsies.

Introduction

Liver cancer is one of the deadliest types of cancer, with a 5-year overall survival rate lower than 20% and death rates increasing around 1.7% each year [1,2]. Hepatocellular carcinoma (HCC) is the most common malignancy of the liver accounting for nearly 90% of all cases [1,3–5]. Major risks of HCC include cirrhosis, viral infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcoholic liver, non-alcoholic fatty liver disease and inherited traits such as metabolic diseases [1,6]. Current HCC diagnostic guidelines report the usage of invasive procedures, such as tissue biopsies, followed by histological and/or contrast-enhanced imaging [7]. This contributes to HCC being often detected in an advanced stage where it is estimated that 40% of the cases are multinodular or expanded beyond the liver leaving patients with limited therapeutic options [5,8]. Screening, surveillance and monitoring programmes are therefore vital to diagnose and detect HCC as early as possible to provide patients with the best treatment possible [9–11]. In addition, HCC patients surgically treated often experience relapses and early detection could bring better management of the disease and increase patient's life quality and span [12].

Body fluids, for example plasma, serum and urine, contain circulating biomarkers that can be measured non-invasively and inexpensively for diagnosis and monitoring of HCC [5,13,14]. Among others, alpha-fetoprotein (AFP) is often proposed as a diagnostic biomarker present in serum or plasma of high-risk individuals for HCC [7,13,15], nonetheless official guidelines indicate that AFP has no diagnostic approved role [3,4]. High levels of AFP are

Here, we perform a systematic discovery of a HCC methylation signature by compiling 1,551 genome-wide DNA methylation arrays from 13 studies [1,31,45,46,49–58], including both tissue and liquid biopsy samples from HCC, cirrhosis and healthy controls. We developed a machine learning pipeline to harness this resource to identify differentially methylated regions (DMRs) predictive of HCC in both tissue and liquid biopsies, from a background of cirrhotic samples. Our approach benchmarked favourably against 12 independent HCC methylation signatures and supported the development of a novel signature comprising 38 DMRs. Some of the identified regions were associated with transcriptional repression of several members of the Zinc Finger Proteins (ZFNs) family suggesting a potential role with cancer progression and early onset. Lastly, we combined the information of the novel DMR signature into a single score which successfully identified HCC tissue samples in an independent dataset (recall 96% and precision 98%), perfectly classified 13 healthy cfDNA samples, and identified 7 (out of 11) tumour cfDNA samples. Of note, the DMR signature score successfully identified cfDNA from diverse tumours, including colorectal and breast cancer, showing its potential as a diagnostic tool for multiple cancers. Overall, we present a systematic discovery and benchmark of methylation biomarkers for the early detection and monitoring of HCC using tissue and liquid biopsies and propose an improved signature and risk score with the potential to be used for non-invasive clinical diagnostics.

Original Article

Gene Silencing and DNA Methylation

P. Parveen*, K. Deepti Brundavani, K. Mahathi, M.S. Bhavani and SK. Shaheda Sultana

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ABSTRACT

This review revealed a new mechanism for gene regulation through "gene silencing" at the transcriptional level (TGS) or at the post-transcriptional level (PTGS), which play a key role in many essential cellular processes. Today dsRNA is used as a powerful tool to experimentally elucidate the function of essentially any gene in a cell. The immense impact of the discovery of RNA interference (RNAi) on biomedical research and its novel medical applications in the future are reviewed in this article, with particular stress on therapeutic applications of radio-labeled antisense oligonucleotides (RASONs) for diagnosis and treatment of various cancers and neurodegenerative diseases by "gene silencing". Antisense oligonucleotides (ASONs) can also modulate alternative splicing which 74% of all human genes undergo. Epigenetic changes affect chromatin structure and thus regulate processes such as transcription, X-chromosome inactivation, allele-specific expression of imprinted genes, and inactivation of tumor suppressor genes. Treatment with inhibitors of DNA methylation and histone deacetylation can reactivate epigenetically silenced genes and has been shown to restore normal gene function. In cancer cells, this results in expression of tumor suppressor genes and other regulatory functions, inducing growth arrest and apoptosis.

Keywords: RNAi, X-chromosome RASONs, DNA methylation, Gene silencing.

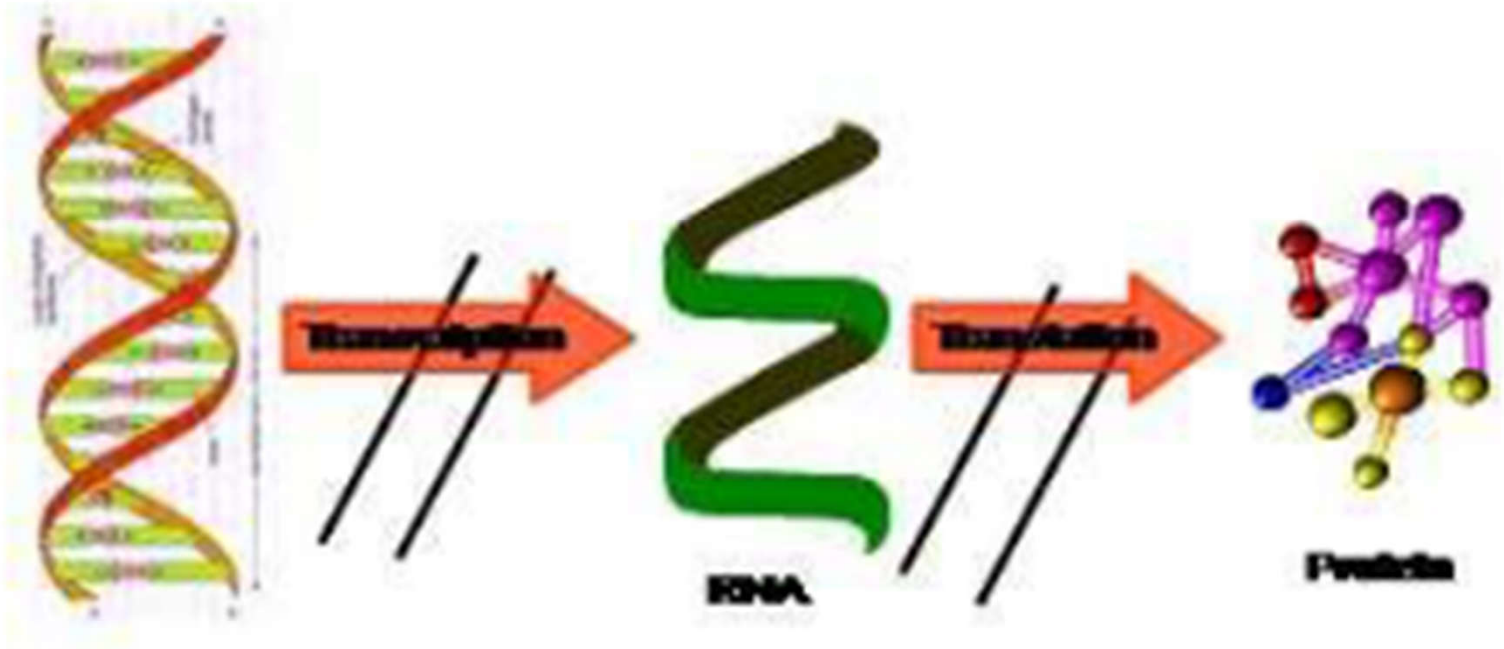


Figure 1. Transcriptional RNA polymerase

CONCLUSION

The biological significance of DNA methylation in the regulation of gene expression and its role in cancer is increasingly recognized. It is now clear that these epigenetic changes affect chromatin structure and thus regulate processes such as transcription, X-chromosome inactivation, allele-specific expression of imprinted genes, and inactivation of tumor suppressor genes. Treatment with inhibitors of DNA methylation and histone deacetylation can reactivate epigenetically silenced genes and has been shown to restore normal gene function. In cancer cells, this results in expression of tumor suppressor genes and other regulatory functions, inducing growth arrest and apoptosis. Azacitidine and decitabine are clinically active in MDS and other hematologic malignancies and may have therapeutic potential in other malignant disorders. Continued clinical trials with hypomethylating agents and HDAC inhibitors, alone or in combination, may provide further advances in the treatment of hematopoietic malignancies and solid tumors.

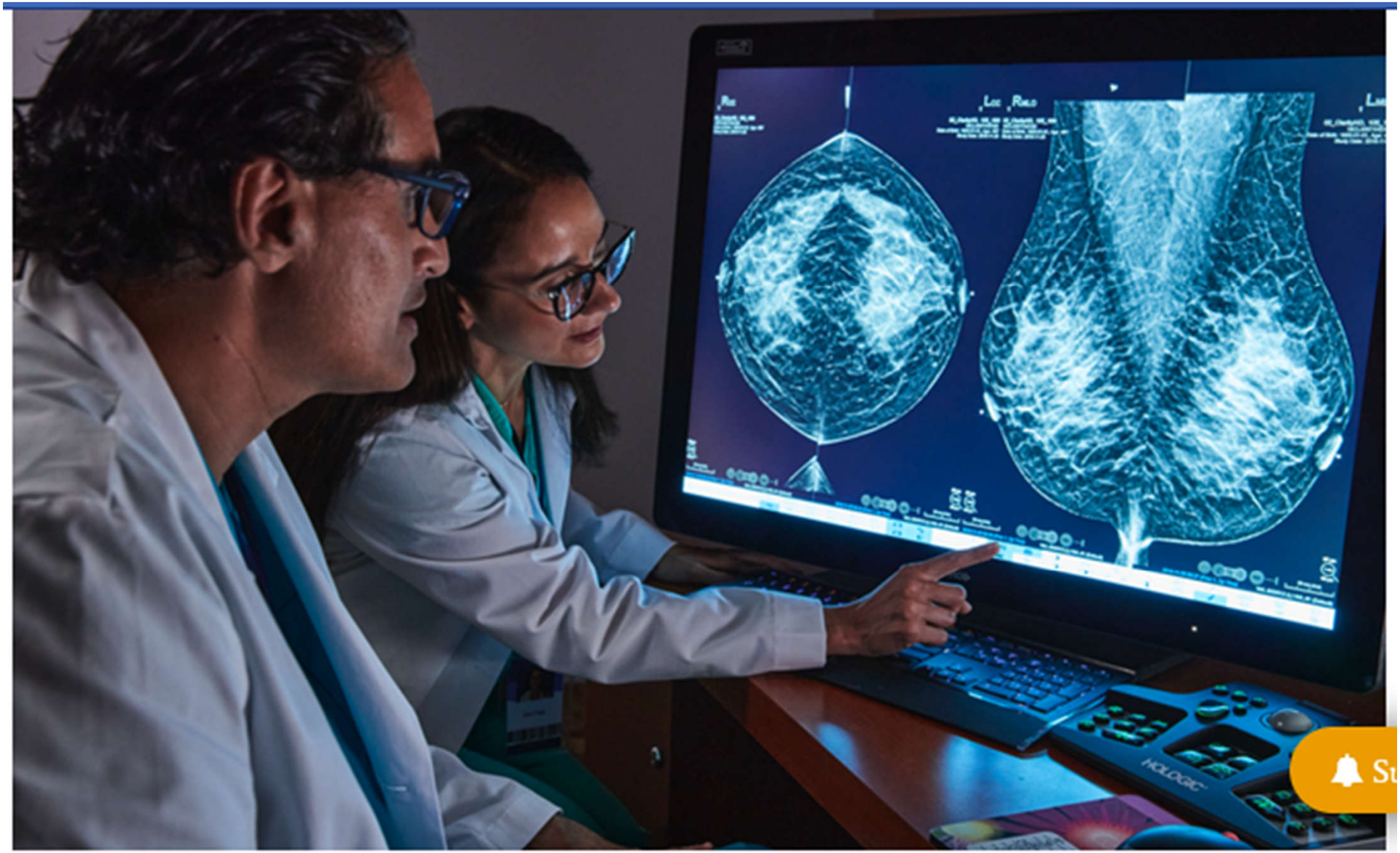
Epigenetics is everywhere you can inherit something beyond DNA sequence that's were the real excitement in genetics now.

IMAGING TECHNOLOGY NEWS

FEATURE | BREAST IMAGING | NOVEMBER 04, 2022 | BY ANDREW SMITH AND PAOLA WISNER

Revolutionizing Women's Health with One-day Diagnosis

Through DBT, medical technology has been able to pave a new path and provide a launch board for AI and other technologies that can use its high-resolution images


HOLOGIC

Today, just over 10 years later, DBT has become the cornerstone of breast cancer screenings, as the technology is proven to have superior clinical performance to 2-D mammography.[1,2] DBT has helped improve cancer detection while at the same time reducing the need for false positive recalls. Since DBT provides layered images for a three-dimensional view of the breast, radiologists benefit from the reduction in overlying tissue that could obscure a lesion — meaning that a mass previously obscured on 2-D exams could be more evident, helping to improve the accuracy of image interpretation.

Just as DBT revolutionized breast screenings, medical technology companies are looking ahead to the next transformation in breast health. For many in the industry, the next major revolution in breast cancer care lies not with one piece of equipment, but rather improvements to the entire patient journey to better integrate screening and diagnosis technologies that work together along the care continuum. These advancements, which could potentially reduce the multiple appointments between screening and diagnosis to one, would subsequently help improve efficiencies for imaging facilities and more importantly, improve the patient experience.

For radiologists, surgeons and doctors, this compression of the timeline could help alleviate backlogs and burnout, while also saving patients anxiety between visits and potentially improving outcomes. For patients, it means women will no longer need to live with uncertainty for the weeks between screening and diagnosis, or balance prioritizing their health with other demands — something that is especially important for those who lack transportation, insurance coverage,

One rapidly evolving innovation with significant potential is **artificial intelligence** (AI), and it is helping to pave the way for improved workflow efficiencies and patient experiences. In mammography, AI is mostly used in assisting radiologists read and prioritize images. When paired with DBT, these AI-powered software tools have become capable of identifying subtle potential cancers that can be mistakenly overlooked, and they can highlight these findings of interest in real time for further examination by the radiologist. With advanced AI algorithms integrated into image processing, radiologists can expedite reading time by reducing the number of images to review, and with no compromise in clinical performance.[4] The pairing of AI and DBT has the potential to improve early detection of breast cancer by providing higher sensitivity, and it can also help optimize workflow by assisting radiologists with categorizing cases in order of suspicion and prioritizing the most concerning patient cases to help optimize care.

Once further developed, AI has the potential to integrate with other forms of technology to help us unlock the solutions to today's breast health challenges. As more research and innovation explores the uses of new technologies, it is possible that, in the years ahead, the time a woman waits between screening and diagnosis could be shortened to a single day.

Subs

Innovating for the Future of Women's Health

We still have ways to go toward achieving the one-day screening to diagnosis model. To reach this goal, the medical technology and device industries need to focus on developing future solutions that optimize detection and treatment of breast cancer lesions and calcifications in all their stages and

Also on the horizon, several medical technology companies are currently investigating minimally invasive treatments with the potential to change the narrative of breast cancer treatment of low-risk cancers that would help facilitate a one-day screening to diagnosis, and possibly treatment, process. These breast conserving techniques may allow treatment of low-risk lesions through a minimally invasive procedure that could be administered in an out-patient setting. Some examples are the use of **cryoablation**, which is a technique that administers liquid nitrogen through a needle to the lesion in order to freeze the cancer, or radiofrequency (RF) ablation which kills the lesion in place through radiofrequency heating. As the cancer cells die, they are then absorbed by the body, limiting the trauma to the body's tissue and improving the conservation of the breast.

DBT has enabled the medical technology industry to pave a new innovative path by providing a launch board for AI and other technologies that can utilize its high-resolution images. Without it, we could not dream of a one-day screening to diagnosis pathway.

There is hope for a future where a one-day model will help identify cancers early so a personalized plan for treatment can be delivered quickly and efficiently. These advancements keep patients center of innovation and development. Just like DBT has become an integral part of women's healthcare, the ongoing research and development into new technologies will help revolutionize **women's health** and set a new standard for care.

Sul

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Droplet digital PCR assay provides intrahepatic HBV cccDNA quantification tool for clinical application

Sanae Hayashi[1,7], Masanori Isogawa[1], Keigo Kawashima[1], Kyoko Ito[1], Natthaya Chuaypen[2], Yuji Morine[3], Mitsuo Shimada[3], Nobuyo Higashi-Kuwata[4], Takehisa Watanabe[7], Pisit Tangkijvanich[2], Hiroaki Mitsuya[4,5,6] & Yasuhito Tanaka[1,7]✉

The persistence of covalently closed circular DNA (cccDNA) poses a major obstacle to curing chronic hepatitis B (CHB). Here, we used droplet digital PCR (ddPCR) for cccDNA quantitation. The cccDNA-specific ddPCR showed high accuracy with the dynamic range of cccDNA detection from 10^1 to 10^5 copies/assay. The ddPCR had higher sensitivity, specificity and precisely than qPCR. The results of ddPCR correlated closely with serum HB core-related antigen and HB surface antigen (HBsAg) in 24 HBV-infected human-liver-chimeric mice (PXB-mice). We demonstrated that in 2 PXB-mice after entecavir treatment, the total cccDNA content did not change during liver repopulation, although the cccDNA content per hepatocyte was reduced after the treatment. In the 6 patients with HBV-related hepatocellular carcinoma, ddPCR detected cccDNA in both tumor and non-tumor tissues. In 13 HBeAg-negative CHB patients with pegylated interferon alpha-2a, cccDNA contents from paired biopsies were more significantly reduced in virological response (VR) than in non-VR at week 48 ($p = 0.0051$). Interestingly, cccDNA levels were the lowest in VR with HBsAg clearance but remained detectable after the treatment. Collectively, ddPCR revealed that cccDNA content is stable during hepatocyte proliferation and persists at quantifiable levels, even after serum HBsAg clearance.

Discussion

In this study, we developed a ddPCR assay for the quantitation of HBV cccDNA, with more sensitivity, specificity and accuracy than qPCR (Figs. 1, 2; Supplementary Fig. S2, S3). The specificity of ddPCR for cccDNA was validated by the assays using the plasmid containing HBV genome and the SB assay (Fig. 2F; Supplementary Fig. S4). The intrahepatic cccDNA was closely correlated with both HBsAg and HBcrAg in the sera of HBV-infected chimeric mice (Fig. 3). Notably, the total amount of cccDNA in the repopulating liver did not change in the absence of active HBV DNA replication during ETV treatment, although the cccDNA content/hepatocyte was reduced by hepatocyte proliferation (Fig. 4). To our knowledge, this is the first study indicating the stability of cccDNA in the proliferating liver, and this novel finding could be obtained because of the high accuracy of ddPCR. The ddPCR was also able to quantitate cccDNA in CHB patients with HCC and those with HBsAg clearance after PEG-IFN treatment (Table 1 and Table S3). Importantly, ddPCR readily quantitated the intrahepatic cccDNA content, even after HBsAg clearance (Fig. 5).

It is generally believed that the amount of cccDNA should be reduced to a very low level to cure HBV infection. Thus, a reliable assay to measure cccDNA is required to evaluate the therapeutic efficacy of new anti-HBV treatments. While qPCR measures the fluorescence signal to determine the amount of DNA in the sample, ddPCR measures the positive and negative fluorescence data from a sample droplet and fits it to a Poisson distribution to measure the endpoint. Therefore, ddPCR reduces the influence of PCR inhibitors, which affect amplification efficiency, and ddPCR is a new technique with improved quantification[4]. Furthermore, ddPCR was reported to be less variable between experiments than qPCR, allowing long-term monitoring[23]. Several recent studies have applied the ddPCR technology to measure HBV cccDNA levels in cultured cells and the livers of CHB patients, and demonstrated the higher sensitivity of ddPCR than qPCR[24–26].

As explained above, several studies both ddPCR and qPCR technologies have already utilized to measure cccDNA using cccDNA-specific primers and probes. However, although the number of mice for this study is small, we believe this is the first study that applied the ddPCR technology to test the impact of hepatocyte proliferation on the stability of cccDNA. We found that the cccDNA content in the liver is extremely stable during 2–3 times of cell division, and this discovery was possible because of the highly sensitive methods such as ddPCR. Previous study has already used the ddPCR method to study the effect of nucleoside analogue on intrahepatic cccDNA levels but did not address the issue of IFN-treated patients[24]. We subsequently showed that our ddPCR can be applied to human samples including HCC and IFN-treated patients.

Although we could not distinguish whether the signals detected in serum of the chimeric mice were false positive rcDNA or cccDNA by SB, cccDNA signals were not detected in negative controls with and without the