

# AMERICAN THORACIC SOCIETY DOCUMENTS

## Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis

### An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Jussi J. Saukkonen\*, Raquel Duarte\*, Sonal S. Munsiff\*, Carla A. Winston\*, Manoj J. Mammen, Ibrahim Abubakar, Carlos Acuña-Villaorduña, Pennan M. Barry, Mayara L. Bastos, Wendy Carr, Hassan Chami, Lisa L. Chen, Terence Chorba, Charles L. Daley, Anthony J. Garcia-Prats, Kelly Holland, Ioannis Konstantinidis, Marc Lipman, Giovanni Battista Migliori, Farah M. Parvez, Adrienne E. Shapiro, Giovanni Sotgiu, Jeffrey R. Starke, Angela M. Starks, Sanket Thakore, Shu-Hua Wang, Jonathan M. Wortham, and Payam Nahid; on behalf of the



## Abstract

**Background:** On the basis of recent clinical trial data for the treatment of drug-susceptible and drug-resistant tuberculosis (TB), the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America have updated clinical practice guidelines for TB treatment in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis.

**Methods:** A Joint Panel representing multiple interdisciplinary perspectives convened with American Thoracic Society methodologists to review evidence and make recommendations using the GRADE (Grading of Recommendations Assessment,

Development and Evaluation) and GRADE-ADOLOPMENT (adoption, adaptation, and, as needed, *de novo* development of recommendations) methodology.

**Results:** New drug-susceptible TB recommendations include the use of a novel 4-month regimen for people with pulmonary TB and a shortened 4-month regimen for children with nonsevere TB. Drug-resistant TB recommendation updates include the use of novel regimens containing bedaquiline, pretomanid, and linezolid with or without moxifloxacin.

**Conclusions:** All-oral, shorter treatment regimens for TB are now recommended for use in eligible individuals.

**Keywords:** tuberculosis; drug-resistant; drug-susceptible; children; adults

Isoniazid	10–15 mg/kg	10–15 mg/kg
Rifampin	10–20 mg/kg	10–20 mg/kg
Pyrazinamide	35 (30–40) mg/kg	None
Ethambutol <sup>§</sup>	20 (15–25) mg/kg (included/excluded based on local guidelines)	None

### Q3: Treatment of Rifampin-Resistant, Fluoroquinolone Resistant TB

#### Recommended BPaL Regimen<sup>¶</sup>

Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk

### Q4: Treatment of Rifampin-Resistant, Fluoroquinolone-Susceptible TB

#### Recommended BPaLM Regimen<sup>¶</sup>

Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk
Moxifloxacin	400 mg daily for 26 wk

<sup>\*</sup>Using actual body weight. Medications should be administered 7 d/wk with food, avoiding milk, antacids, or other cationic items, with DOT 5 of 7 days per week.

<sup>†</sup>Pyridoxine (vitamin B<sub>6</sub>), 25–50 mg/d, should be given with isoniazid to all patients.

<sup>‡</sup>Using actual body weight and DOT 5 of 7 days per week.



## Review

# Deciphering breast cancer: from biology to the clinic

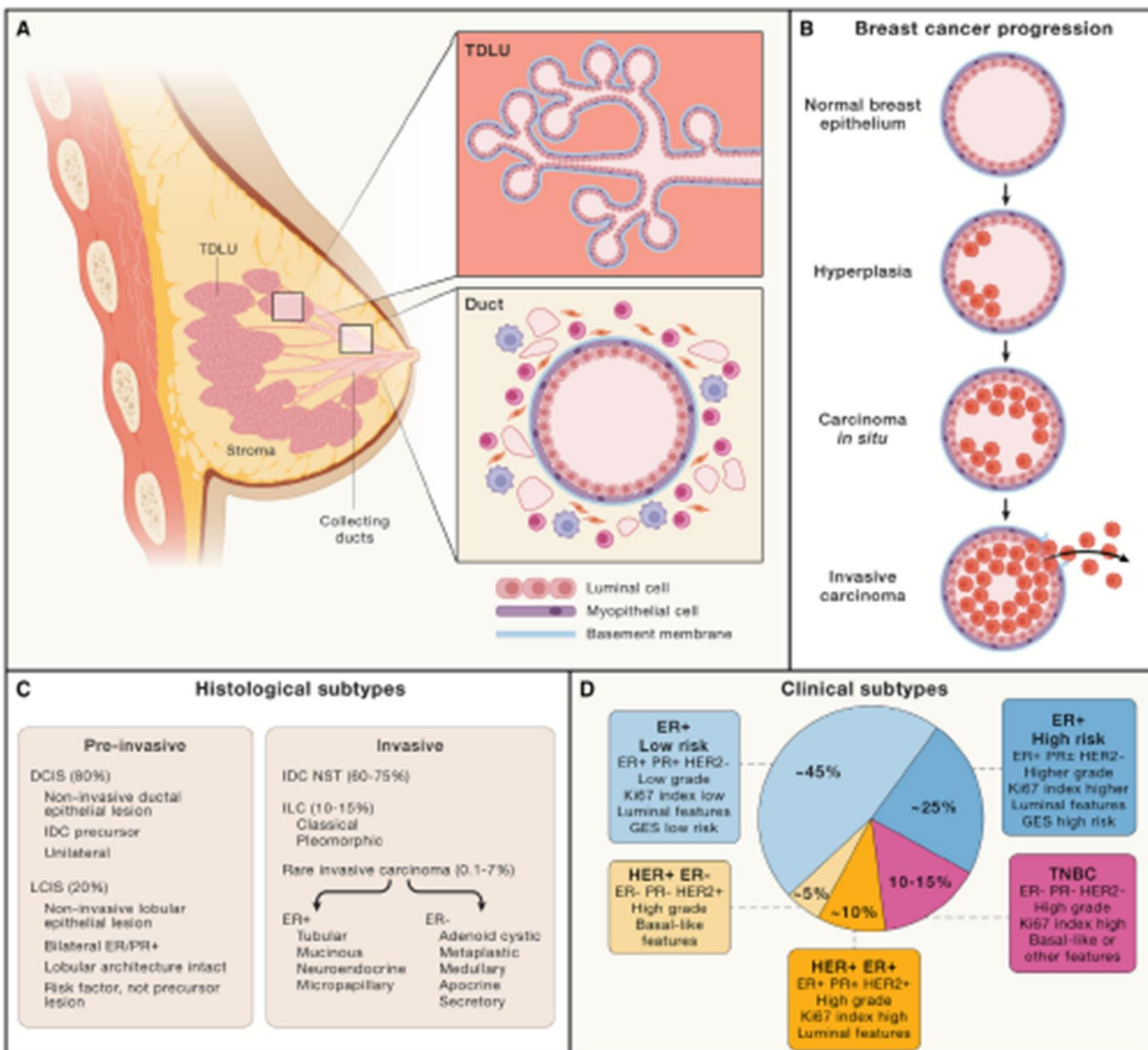
Emma Nolan,<sup>1</sup> Geoffrey J. Lindeman,<sup>2,3,4,6</sup> and Jane E. Visvader

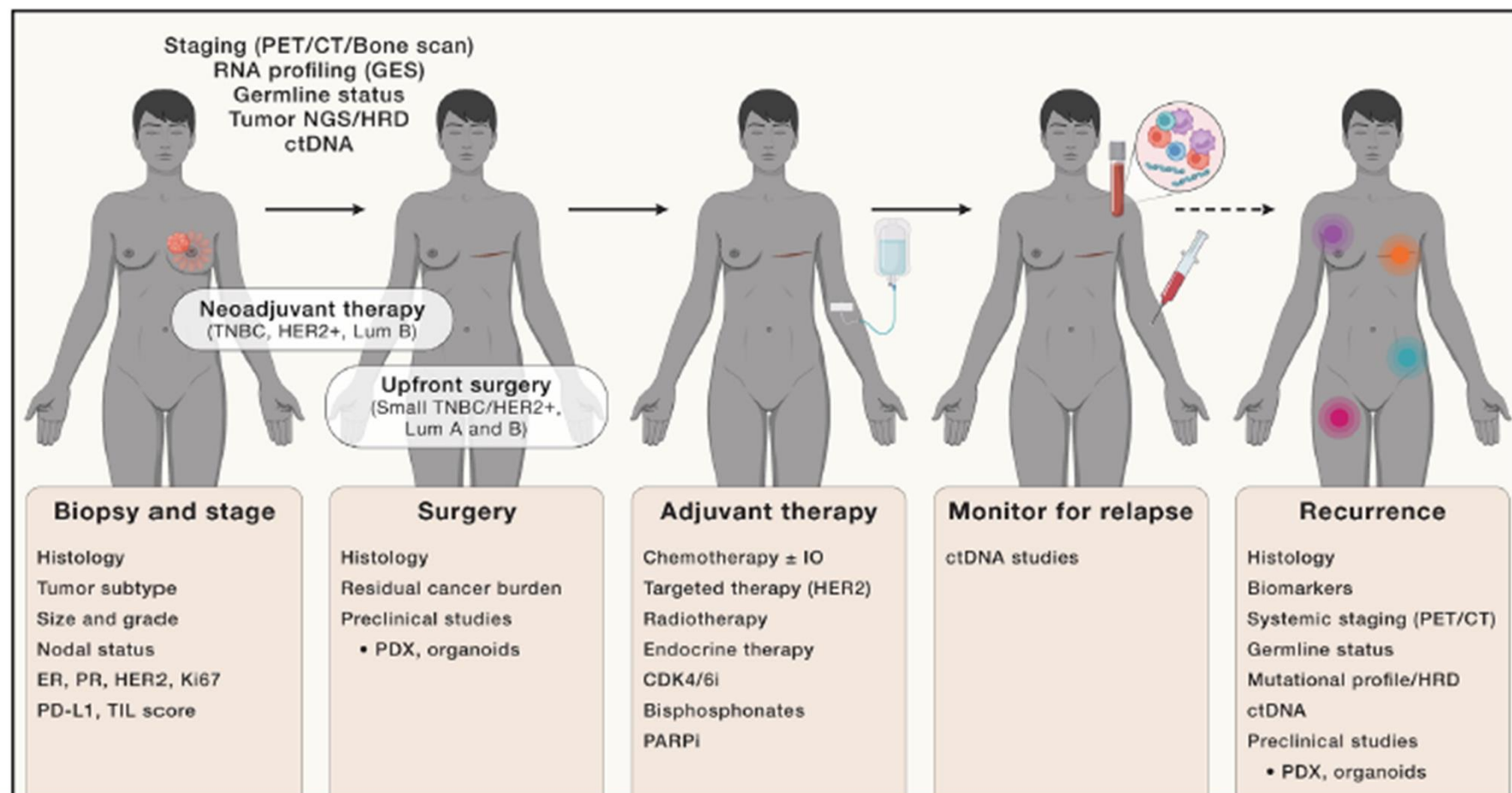
<sup>1</sup>Auckland Cancer Society Research Centre, University of Auckland, Au

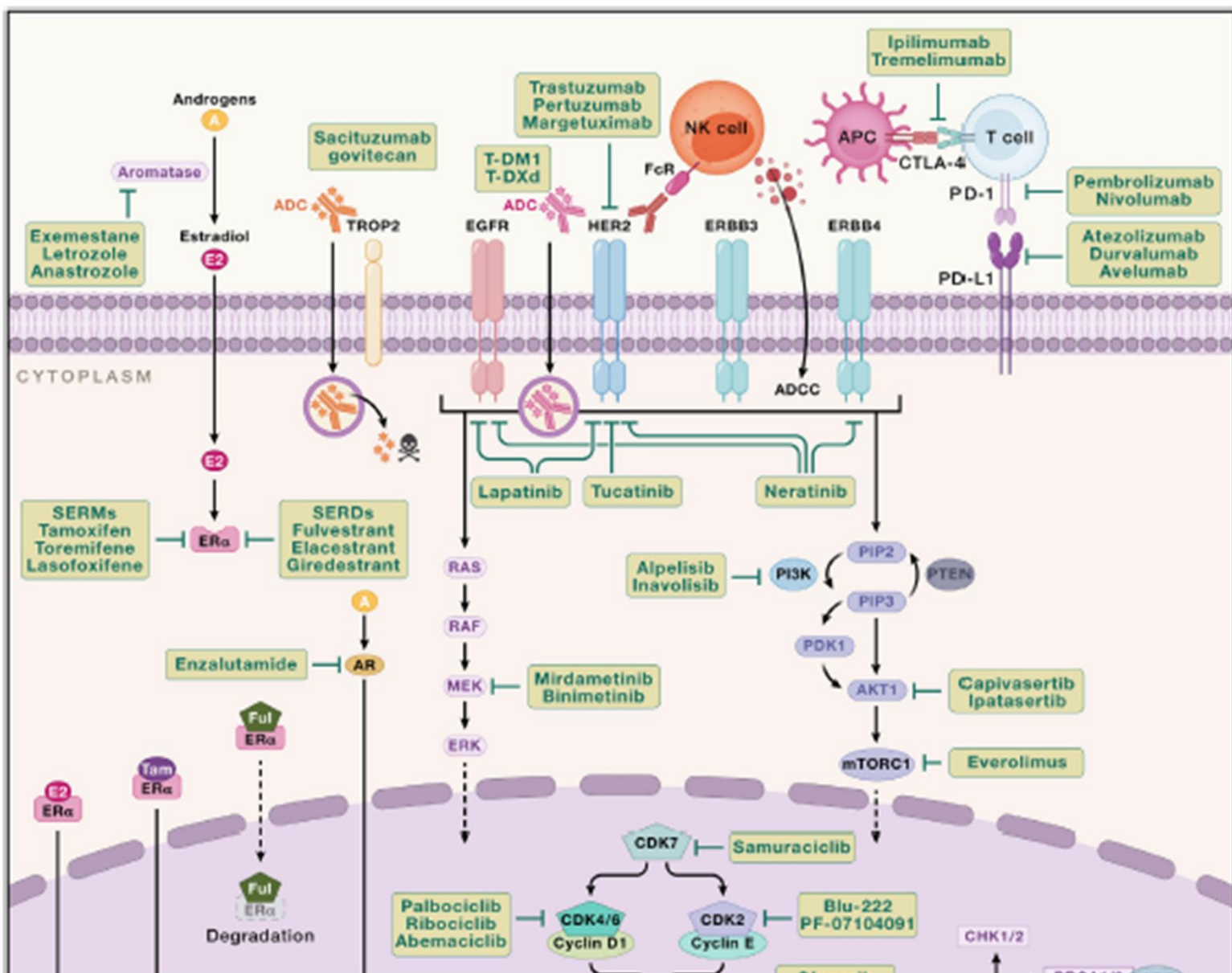
<sup>2</sup>ACRF Cancer Biology and Stem Cells Division, The Walter and Eliza H

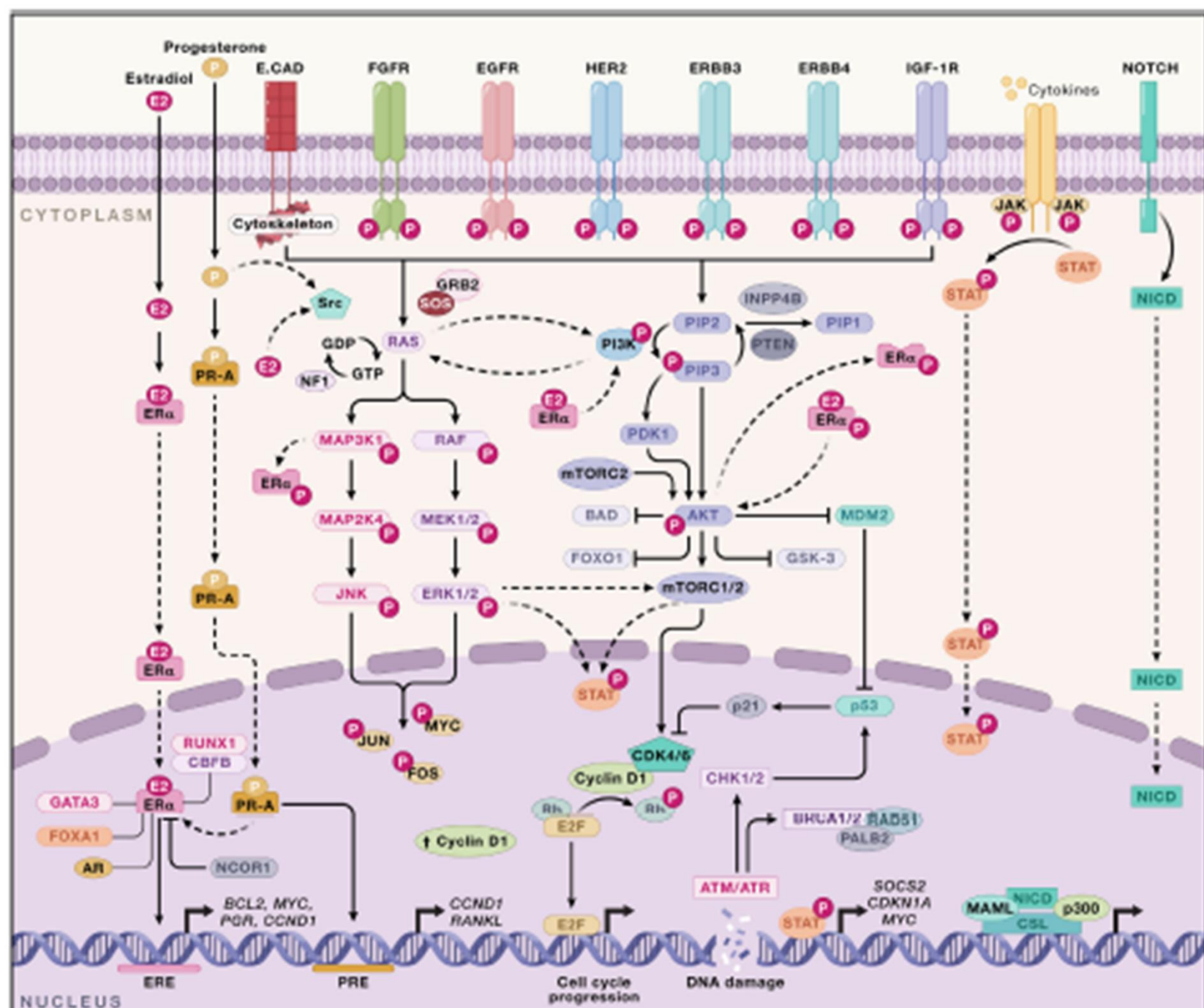
## SUMMARY

Breast cancer remains a leading cause of cancer-related mortality in women, reflecting profound disease heterogeneity, metastasis, and therapeutic resistance. Over the last decade, genomic and transcriptomic data have been integrated on an unprecedented scale and revealed distinct cancer subtypes, critical molecular drivers, clonal evolutionary trajectories, and prognostic signatures. Furthermore, multi-dimensional integration of high-resolution single-cell and spatial technologies has highlighted the importance of the entire breast cancer ecosystem and the presence of distinct cellular “neighborhoods.” Clinically, a plethora of new targeted therapies has emerged, now being rapidly incorporated into routine care. Resistance to therapy, however, remains a crucial challenge for the field.











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Tools

be a notable lack of recurrently mutated and targetable pathways. For such cancers where chromosomal instability is a driving force, targeting mechanisms that underlie genomic instability may be necessary. The functional importance of many aberrations and genetic dependencies across the different breast cancer subtypes remain to be determined. This demands comprehensive functional screening (e.g., using CRISPR-Cas9 editing) combined with deeper analyses and data integration to deconvolve pivotal molecular pathways and interconnecting nodes. Despite the wealth and depth of genetic information now available for breast cancer, translation into precision medicine and routine clinical practice remains an ongoing challenge. Nevertheless, the continuing refinement and integration of genomic and expression signatures with clinico-pathological features has dramatically expanded our understanding of mechanisms underpinning breast cancer and should ultimately lead to improved biomarker tools to guide treatment escalation and de-escalation. Novel approaches to personalizing therapy should also benefit further from the application of multi-omics machine learning, recently shown to predict response to therapy (Sammut et al., 2022).

Revolutionary advances in single-cell technologies and computational analysis have paved the way for dissection of tissue heterogeneity and clonal evolution for breast cancer at remarkable resolution. However, the true extent and impact of heterogeneity on clinically relevant parameters such as prognosis and therapy prediction and on tumor evolution are yet to be determined. A further caveat to single-cell RNA-seq studies is that different stringencies have been applied for cluster analysis, leading to variable data. It is important to note that without a functional readout, the relevance of the different clusters/subsets remains unresolved. The emergence of drug resistance continues to pose a major barrier to the efficacy of therapies.

## ACKNOWLEDGMENTS

Due to space constraints, it was not possible to cite many publications, and we apologize for these omissions. E.N. is supported by the Auckland Medical Research Foundation's Douglas Goodfellow Repatriation Fellowship (1421001). G.J.L. and J.E.V. are supported by the National Health and Medical Research Council (NHMRC #1175960 and 1194605), National Breast Cancer Foundation (NBCF, IIRS-19-004 and IIRS-20-022), and the Breast Cancer Research Foundation (to G.J.L.).

## DECLARATION OF INTERESTS

G.J.L. has had consulting/advisory roles with AbbVie and Pfizer and received institutional support for investigator-initiated clinical trials from Amgen, AbbVie, Genentech (Roche), and Pfizer. The Walter and Eliza Hall Institute of Medical Research receives milestone and royalty payments related to venetoclax. Employees are entitled to receive benefits related to these payments; G.J.L. and J.E.V. report receiving benefits.

## REFERENCES

- Agus, D.B., Akita, R.W., Fox, W.D., Lewis, G.D., Higgins, B., Pisacane, P.I., Lofgren, J.A., Tindell, C., Evans, D.P., Maiese, K., et al. (2002). Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. *Cancer Cell* 2, 127–137. [https://doi.org/10.1016/s1535-6108\(02\)00097-1](https://doi.org/10.1016/s1535-6108(02)00097-1).
- All, H.R., Jackson, H.W., Zanotelli, V.R.T., Danenberg, E., Fischer, J.R., Bardwell, H., Provenzano, E., All, H.R., Sa, A'd, M., Alon, S., et al. (2020). Imaging mass cytometry and multiplexed genomics define the phenogenomic landscape of breast cancer. *Nat. Cancer* 1, 163–175. <https://doi.org/10.1038/s43018-020-0026-6>.
- Andersson, A., Larsson, L., Stenbeck, L., Salmén, F., Ehinger, A., Wu, S.Z., Al-Eryani, G., Roden, D., Swarbrick, A., Borg, Å., et al. (2021). Spatial deconvolution of HER2-positive breast cancer delineates tumor-associated cell type interactions. *Nat. Commun.* 12, 6012. <https://doi.org/10.1038/s41467-021-26271-2>.
- André, F., Grueiro, E., Rubovszky, G., Campone, M., Loibl, S., Rugo, H.S., Iwata, H., Conte, P., Mayer, I.A., Kaufman, B., et al. (2019). Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer.

ORIGINAL ARTICLE **OPEN ACCESS**

# Successful Amendment of an Existing Hepatitis B Screening Programme by a Guideline Recommended Hepatitis D Screening in the Primary Care Setting

Toni Herta<sup>1,2,3</sup>  | Anna Joachim-Richter<sup>4</sup> | David Petroff<sup>5</sup>  | Benno Wölk<sup>4</sup> | Ingmar Wolfram<sup>6</sup> | Thomas Berg<sup>1</sup> | Jan Kramer<sup>4</sup> | Olaf Bätz<sup>4</sup> | Johannes Wiegand<sup>1</sup> 

<sup>1</sup>Division of Hepatology, Department of Medicine II, Leipzig University Medical Center, Leipzig, Germany | <sup>2</sup>Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum and Campus Charité Mitte, Charité-Universitätsmedizin Berlin, Berlin, Germany | <sup>3</sup>Berlin Institute of Health at Charité—Universitätsmedizin Berlin, BIH Biomedical Innovation Academy, BIH Charité Clinician Scientist Program, Berlin, Germany | <sup>4</sup>LADR



## ABSTRACT

**Background:** Despite European guidelines recommending anti-hepatitis D virus (HDV) screening for all hepatitis B surface antigen (HBsAg)-positive cases, screening rates remain insufficient.

**Aims:** We analysed anti-HDV screening rates in primary care and implemented prospective HDV screening in HBsAg-positive cases identified in the preventive medical examination from the age of 35 ("Check-Up 35+").

**Methods:** From 2012 to 2021, we reviewed anti-HDV and HDV RNA test rates in HBsAg-positive patients at 11 sites of a large German laboratory group. From 2022 to 2023, we prospectively screened HBsAg-positive samples from the "Check-Up 35+" for anti-HDV. Anti-HDV positive patients were then contacted again for HDV RNA testing.

**Results:** Retrospectively, 2792/13,905 (20%) HBsAg-positive cases were tested for anti-HDV, with 142/2792 (5.1%) being positive. HDV RNA was tested in 57/142 (40%) anti-HDV-positive cases, with 26/57 (46%) being positive. In the prospective screening, 1159/225,901 (0.51%) individuals were HBsAg-positive. Of these, 700 (60%) were tested for anti-HDV, with 18/700 (2.6%) positive test results. 4/18 (22%) were successfully contacted again for HDV RNA analysis, with one case testing positive. Neither the HBsAg nor the anti-HDV positive result was known prior to screening in these cases. Anti-HDV testing could not be performed in 459/1159 (40%) HBsAg-positive cases, primarily due to insufficient blood sample volume (310/459 cases, 68%), with others missed due to logistical errors.

# Radiology

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Gastrointestinal Imaging

## Gadoxetic Acid-enhanced MRI Scoring Model to Predict Pathologic Features of Hepatocellular Carcinoma

 Kun Zhang\*,  Kan He\*,  Lei Zhang,  Wen-Cui Li,  Shuang-Shuang Xie,  Ying-Zhu Cui,

## Results

A total of 366 patients (median age, 57 years [IQR, 49–64 years]; 314 men, 52 women) from the three centers were included in the training dataset ( $n = 150$ ), two external validation datasets ( $n = 73$  and  $56$ ), and outcome dataset ( $n = 87$ ). The area under the receiver operating characteristic curve (AUC) of the I-score for predicting high-risk pathologic features was 0.93 (95% CI: 0.88, 0.97) in the training dataset and 0.86 (95% CI: 0.76, 0.93) and 0.84 (95% CI: 0.72, 0.92) in the two external datasets. In the outcome dataset, the I-score was an independent predictor of early recurrence (hazard ratio, 5.2 [95% CI: 1.9, 14.2];  $P = .002$ ). A combined model including the I-score and two other predictors demonstrated superior prognostic performance (C index, 0.84 [95% CI: 0.74, 0.91]).

## Conclusion

The developed scoring model based on gadoxetic acid-enhanced MRI enabled noninvasive preoperative prediction of HCC high-risk pathologic features and early recurrence.

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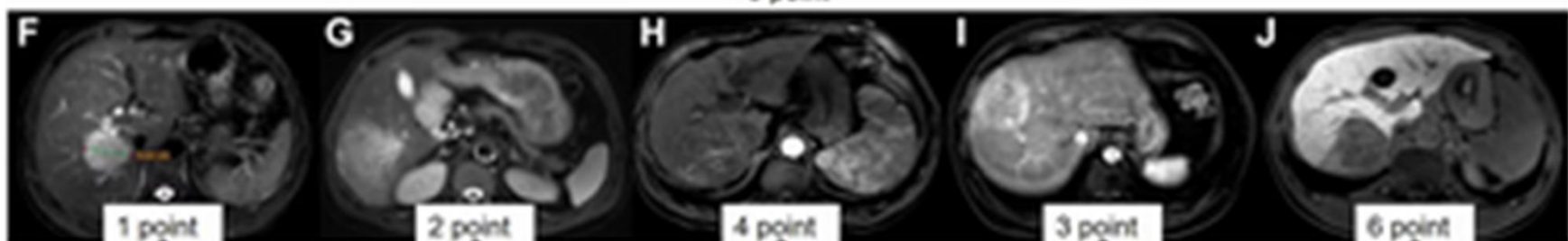


*Morphological and intratumoral features*

*Peritumoral features*



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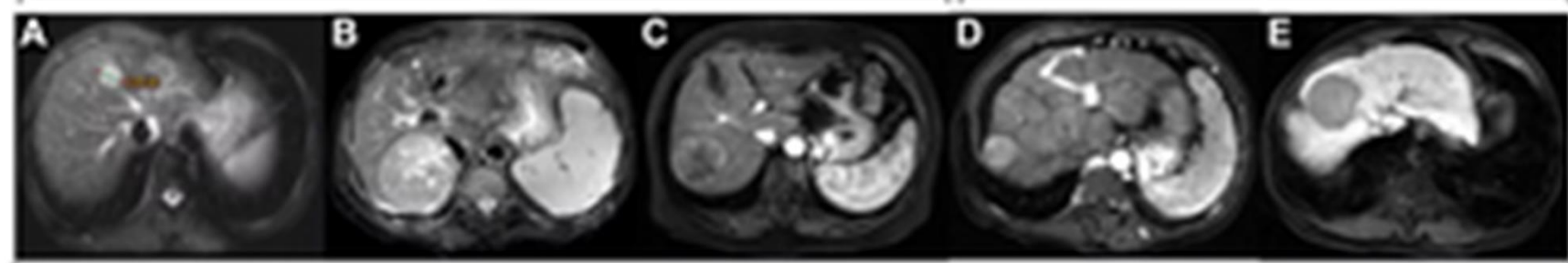
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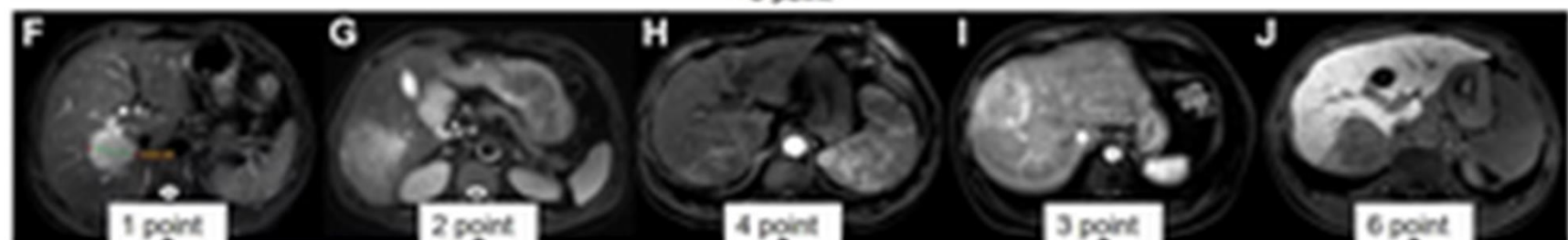
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*Morphological and intratumoral features*

*Peritumoral features*



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**I-score**



## HHS Public Access

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### **Current Best Practice in Hepatitis B Management & Understanding Long-Term Prospects for Cure**

David Yardeni<sup>1</sup>, Kyong-Mi Chang<sup>2</sup>, Marc G. Ghany<sup>1</sup>

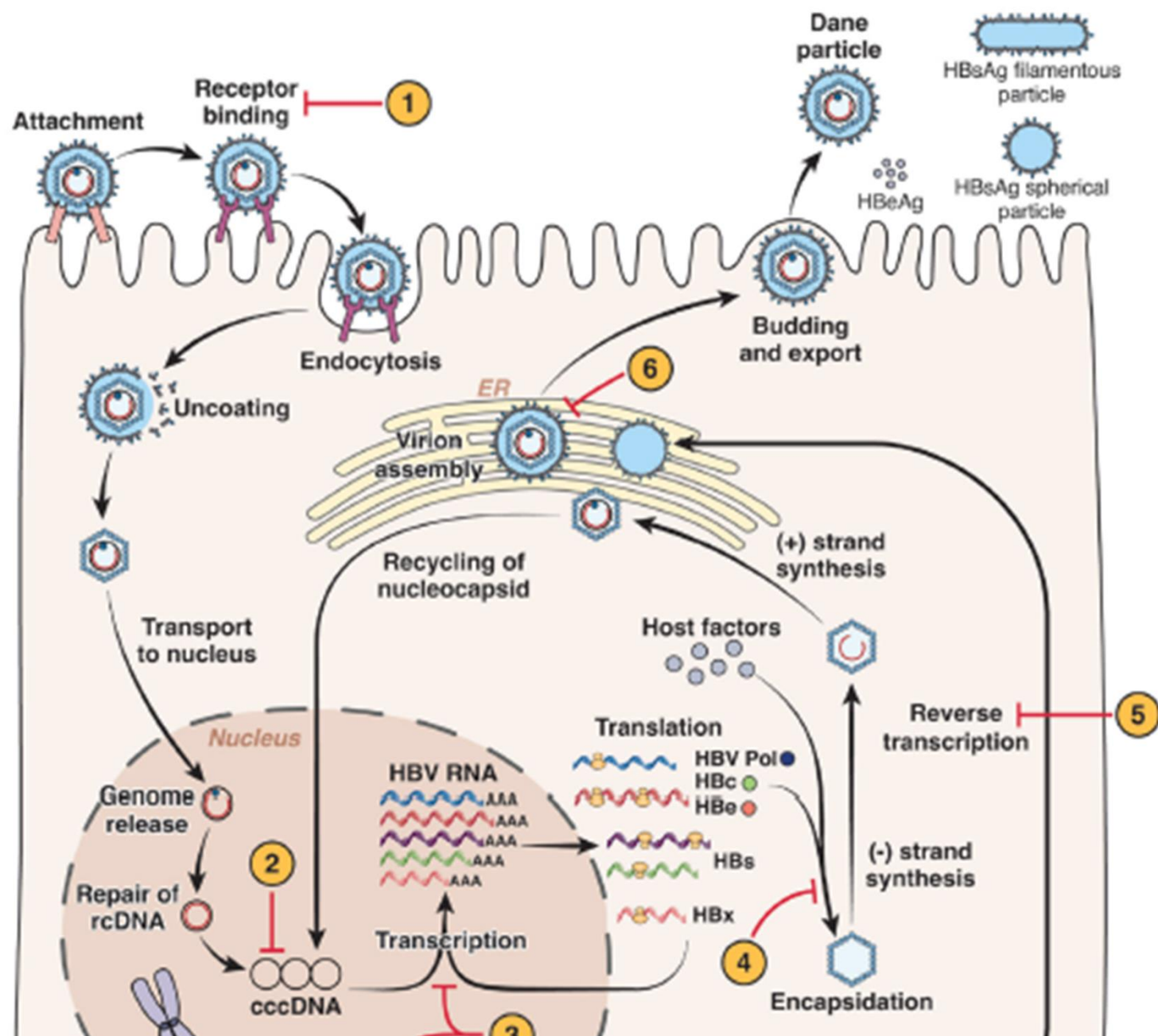
<sup>1</sup>Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

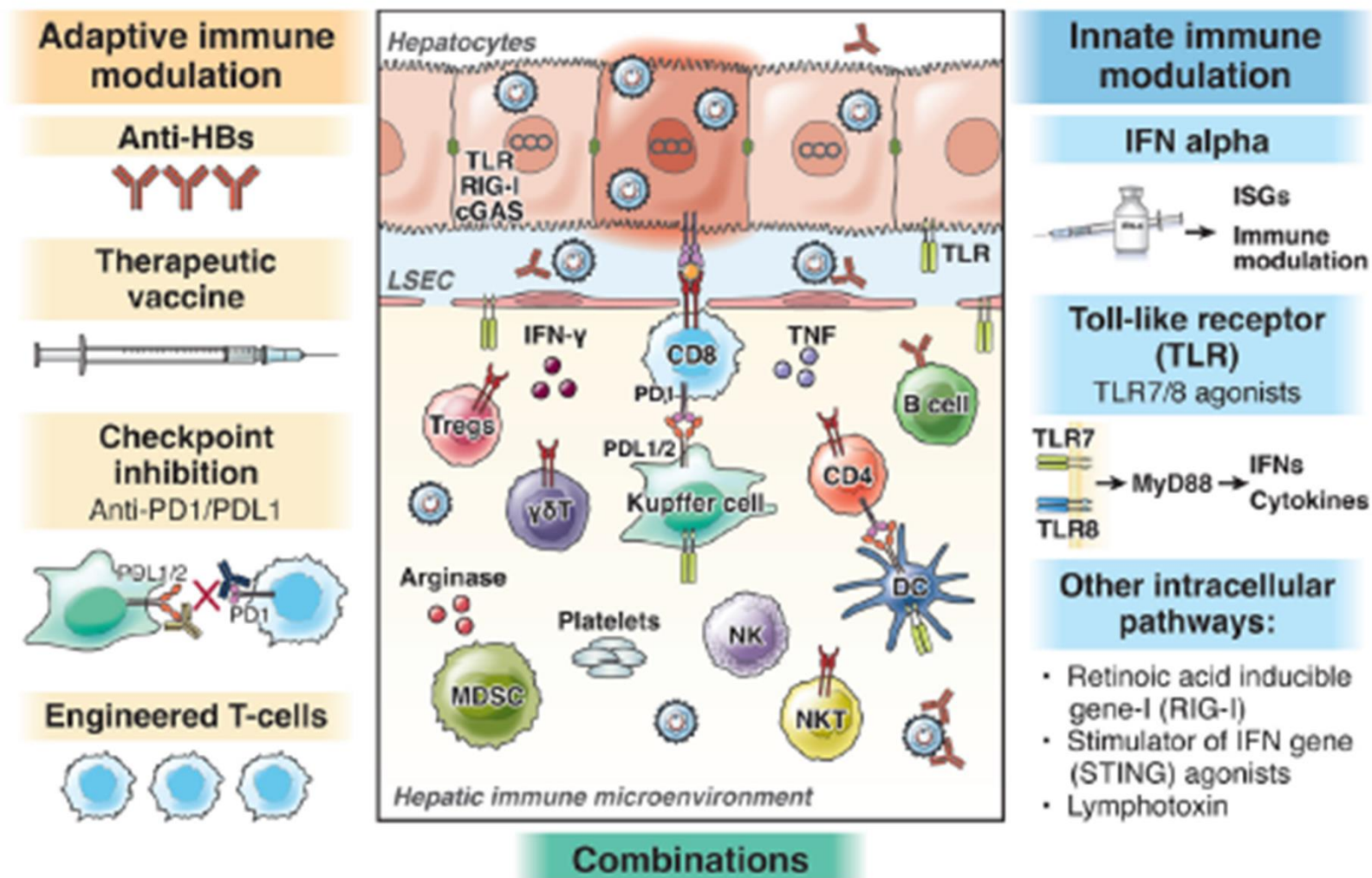
<sup>2</sup>Medical Research, Corporal Michael J. Crescenz VA Medical Center & Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

## Abstract

The hepatitis B virus (HBV) is a major cause of cirrhosis and hepatocellular carcinoma worldwide. Despite an effective vaccine the prevalence of chronic infection remains high. Current therapy is effective at achieving on-treatment but not off-treatment viral suppression. Loss of hepatitis B surface antigen (HBsAg), the best surrogate marker of off-treatment viral suppression, is associated with improved clinical outcomes. Unfortunately, this endpoint is rarely achieved with current therapy because of their lack of effect on covalently closed circular DNA, the template of viral transcription and genome replication. Major advancements in our understanding of HBV virology along with better understanding of immunopathogenesis have led to the development of a multitude of novel therapeutic approaches with the prospect of achieving functional cure (HBsAg loss) and perhaps complete cure (clearance of cccDNA and integrated HBV DNA). This review will cover current best practice for managing chronic HBV infection and emerging novel therapies for HBV infection and their prospect for cure.

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Target	Mechanism of Action	Agent in Development	Current Stage of Development
	TLR 8 agonist	GS-9688	Phase 2
		SBT 8230	Preclinical
Adaptive immunity	Checkpoint inhibitor	Nivolumab	Phase 2
		Emvafolimab (ASC22)	Phase 2
	Immune Mobilizing Monoclonal T-cell Receptors Against Virus (ImmTAV)	IMC-II109V	Phase 1/2
Therapeutic vaccines	DNA vaccines	GS-4774	Phase 2
		HB-110	Phase 1
		DNO-1800/9112	Phase 1
		JNJ-64300535	Phase 1
		MVA-HBV (VTP-300)	Phase 1
		TG1050	Phase 1
		VRON-0200	Preclinical
	T-cell or B-cell epitope vaccine	ePA-44	Phase 3
		FP-02.2 (HepTcell)	Phase 2
	HBV envelope antigen vaccines	NASVAC	Phase 4
		BRII-179	Phase 2
		VVX001	Phase 2

NTCP, sodium taurocholate co-transporting polypeptide; HBX, HBV X protein; HBsAg, HBV surface antigen; cccDNA, covalently closed circular DNA; siRNA, small interfering RNAs; ASO, antisense oligonucleotides.

\* For HBV/HDV co-infection not HBV monotherapy.

## Indications for Treatment by Liver Society Guidelines and World Health Organization.

Indication	AASLD	EASL	APASL	WHO
Cirrhosis (any detectable HIV DNA)	Treat	Treat	Treat	Treat
HIVAg positive CHB	Treat if: ALT <sub>2</sub> ≥ 2 X ULN and HIV DNA > 20,000 IU/mL	Treat if: HIV DNA > 2,000 IU/mL, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis*	Treat if: a. HIV DNA > 20,000 IU/mL and ALT > 2 X ULN (if no concern of hepatic decompensation, observe) b. HIV DNA > 20,000 IU/mL and ALT > 2 ULN, treat if moderate to severe inflammation or fibrosis*. c. HIV DNA < 20,000 and any ALT treat if moderate to severe inflammation or fibrosis*.	Treat all adults above the age of 50 if: a. HIV DNA > 20,000 IU/mL and ALT > ULN (tested 3 times during a 6–12-month period) b. ALT > ULN and other causes of ALT elevation have been excluded (if HIV DNA testing unavailable c)
HIVAg negative CHB	Treat if: ALT <sub>2</sub> ≥ 2 X ULN and HIV DNA > 2,000 IU/mL	Treat if: HIV DNA > 2,000 IU/mL, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis*	Treat if: a. HIV DNA > 2,000 IU/mL and ALT > 2 X ULN (if no concern of hepatic decompensation, observe) b. HIV DNA > 2,000 IU/mL and ALT > 2 X ULN, treat if moderate to severe inflammation or fibrosis*. HIV DNA < 2,000 IU/mL, treat if moderate to severe inflammation or fibrosis*.	
CHB reactivation	Treat	Treat	Treat	Treat
Pregnant women with HIV DNA > 200,000 IU/mL on 3 <sup>rd</sup> trimester	Treat	Treat	Treat**	Decision to treat should be based on regular treatment indications. No specific recommendation regarding prevention of vertical transmission

<sup>1</sup> Normal ALT defined as >5 and <25 U/L for males and females, respectively.

<sup>2</sup> Normal ALT defined as ≤ laboratory upper limit of normal (~40 U/L).

\* Based on histologic assessment of liver biopsy including moderate to severe inflammation by either Ishak activity score >3 or METAVIR activity score above A2. Fibrosis by Ishak score > 3 or METAVIR >2, Elastography (Fibroscan®) > 8kPa.

\*\* If HIV DNA is above 6–7 log IU/mL.

ALT, alanine aminotransferase; AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of the Liver; APASL, Asian-Pacific Association for the Study of Liver Disease; WHO, World Health Organization.

HBeAg positive	PegIFN (180mcg/week SC)	Entecavir (0.5mg/day PO)	Tenofovir disoproxil fumarate (245– 300mg/day PO)	Tenofovir alafenamide (25mg/day PO)
Anti-HBeAg seroconversion	32% <sup>1</sup>	21% <sup>2</sup> 23% <sup>3</sup>	21% <sup>2</sup> 27% <sup>4</sup>	10% <sup>2</sup>
HBV DNA < 60–80 IU/mL	14% <sup>1</sup>	67% <sup>2</sup> 94% <sup>3</sup>	76% <sup>2</sup> 98% <sup>4</sup>	64% <sup>2</sup>
ALT normalization	41% <sup>1</sup>	68% <sup>2</sup> 80% <sup>3</sup>	68% <sup>2</sup> 78% <sup>4</sup>	72% <sup>2</sup>
HBsAg loss	3–7% <sup>1</sup>	2% <sup>2</sup> 1.4% <sup>3</sup>	3% <sup>2</sup> 5% <sup>4</sup>	1% <sup>2</sup>
HBeAg negative	PegIFN (180mcg/week)	Entecavir (0.5mg/day)	Tenofovir disoproxil fumarate (245–300mg/ day)	Tenofovir alafenamide (25mg/day)
HBV DNA < 60–80 IU/mL	19% <sup>1</sup>	90% <sup>2</sup>	93% <sup>2</sup> 100% <sup>4</sup>	94% <sup>2</sup>
ALT normalization	59% <sup>1</sup>	78% <sup>2</sup>	76% <sup>2</sup> 83% <sup>4</sup>	83% <sup>2</sup>
HBsAg loss	4% <sup>1</sup>	0% <sup>2</sup>	0% <sup>2</sup> 3% <sup>4</sup>	0% <sup>2</sup>

Table adapted from EASL Clinical practice guidelines J Hepatol 2017; 67:370–398 and Terrault N et al Hepatology 2018; 67:1560–1599.

pegIFN, pegylated interferon alfa-2a; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B s antigen; ALT, alanine aminotransferase.

THE END