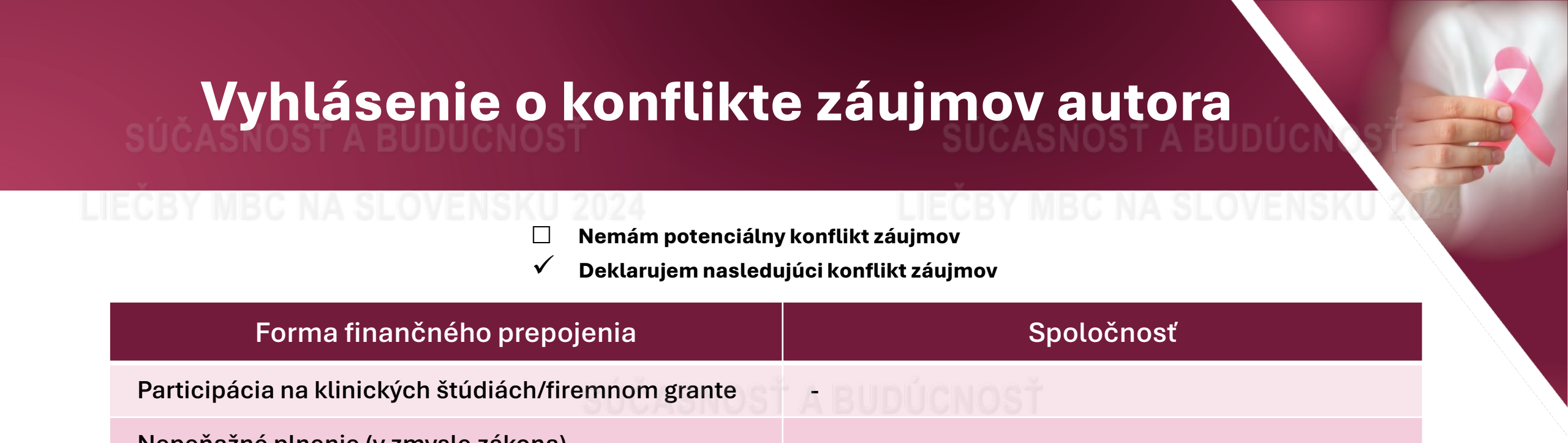
Zmeny hodnotenia (a reportovania) stavu HER2 v tkanive metastatického karcinómu prsníka

Lukáš Plank

Ústav patologickej anatómie JLF UK a UN v Martine
a
Martinské bioptické centrum s.r.o.,
prevádzka patológie a molekulárnej genetiky v Martine

Vyhlásenie o konflikte záujmov autora



☐ **Nemám potenciálny konflikt záujmov**

✓ **Deklarujem nasledujúci konflikt záujmov**

Forma finančného prepojenia	Spoločnosť
Participácia na klinických štúdiách/firemnom grante	-
Nepeňažné plnenie (v zmysle zákona)	-
Prednášajúci	AstraZeneca
Akcionár	-
Konzultant/odborný poradca	-
Ostatné príjmy (špecifikovať)	-

Podľa UEMS (upravené v zmysle slovenskej legislatívy)

Účelom prednášky nie je reklama liekov. Jej účelom je výlučne zdieľanie výsledkov klinických štúdií, výmena skúseností z klinickej praxe a podpora odbornej medicínskej diskusie.

Prezentácia je podporená spoločnosťou AstraZeneca.
Spoločnosť nezasahovala do odborného obsahu a štruktúry s výnimkou overenia súladu obsahu s požiadavkami legislatívy.

SK-2240

„Motto“ prezentácie

- **The integration of cancer biomarkers into oncology has revolutionized cancer treatment, yielding remarkable advancements in cancer therapeutics and the prognosis of cancer patients.**

- **The development of personalized medicine represents a turning point and a new paradigm in cancer management, as biomarkers enable oncologists to tailor treatments based on the unique molecular profile of each patient’s tumor.**

Passaro A et al., Cell 2024, https://doi.org/10.1016/j.cell.2024.02.041

Molekulová klasifikácia a HER2 biomarker: prognostický a prediktívny význam

special article

Annals of Oncology 22: 1736–1747, 2011
doi:10.1093/annonc/mdr304
Published online 27 June 2011

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

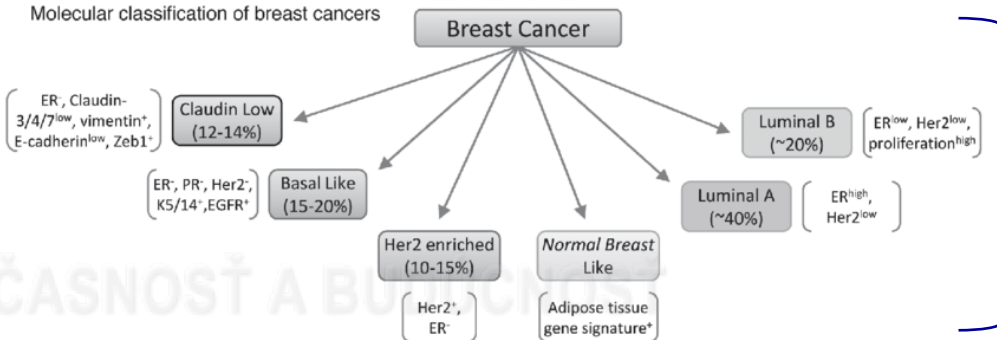
A. Goldhirsch[1*], W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. Senn[6] & Panel members[†]

Intrinsic Subtype (1)	Clinico-pathologic definition
Luminal A	'Luminal A'
	ER and/or PgR positive(76)
	HER2 negative (77)
	Ki-67 low (<14%)*
Luminal B**	'Luminal B (HER2 negative)'
	ER and/or PgR positive
	HER2 negative
	Ki-67 high
	'Luminal B (HER2 positive)'
	ER and/or PgR positive
	Any Ki-67
	HER2 over-expressed or amplified
Erb-B2 overexpression	'HER2 positive (non luminal)'
	HER2 over-expressed or amplified
	ER and PgR absent
'Basal-like'	'Triple negative (ductal)'
	ER and PgR absent
	HER2 negative

Goldhirsch A et al., Annals of Oncology 22: 1736–1747, 2011

WHO klasifikácia nádorov prsnej žľazy (5. vyd.)

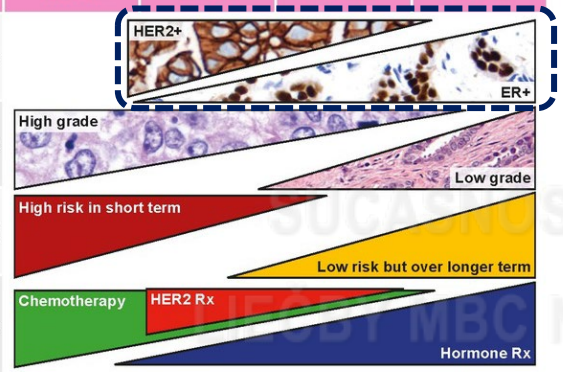
Pre prax zjednodušená molekulová klasifikácia = expresia ER, PR, HER2



- **Luminal A**
- **Luminal B**
- **HER2+**
- **TNBC**

Korelácia s klinicko-patologickými črtami

Molecular Subtypes:	Basal	HER2-E	Luminal B	Luminal A
% of breast cancers:	15-20%	10-20%	20-30%	40-60%
Receptor expression:				
Histologic grade:				
Recurrence risk:				
Therapies used:				

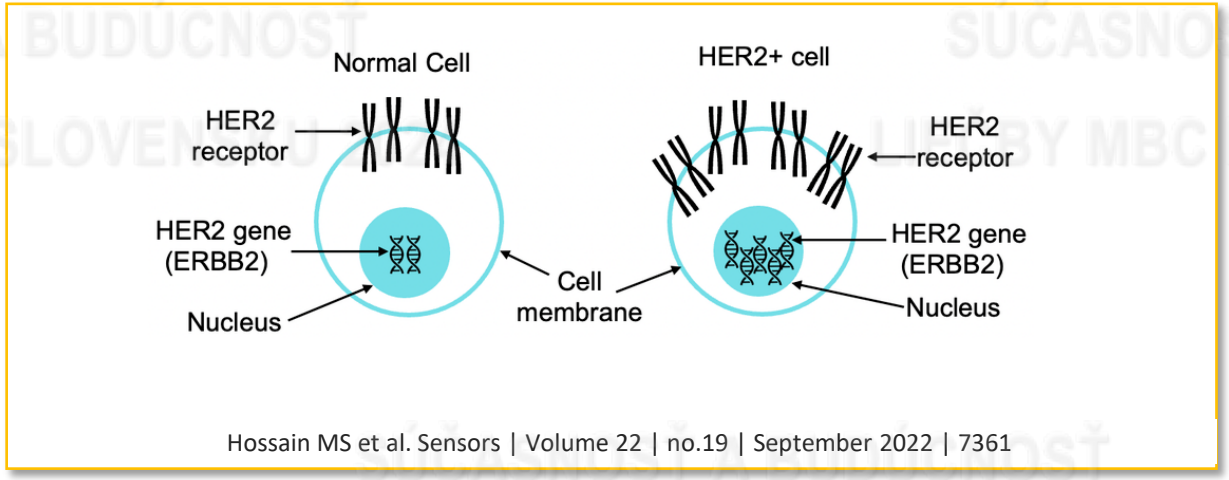


Pre voľbu liečby:

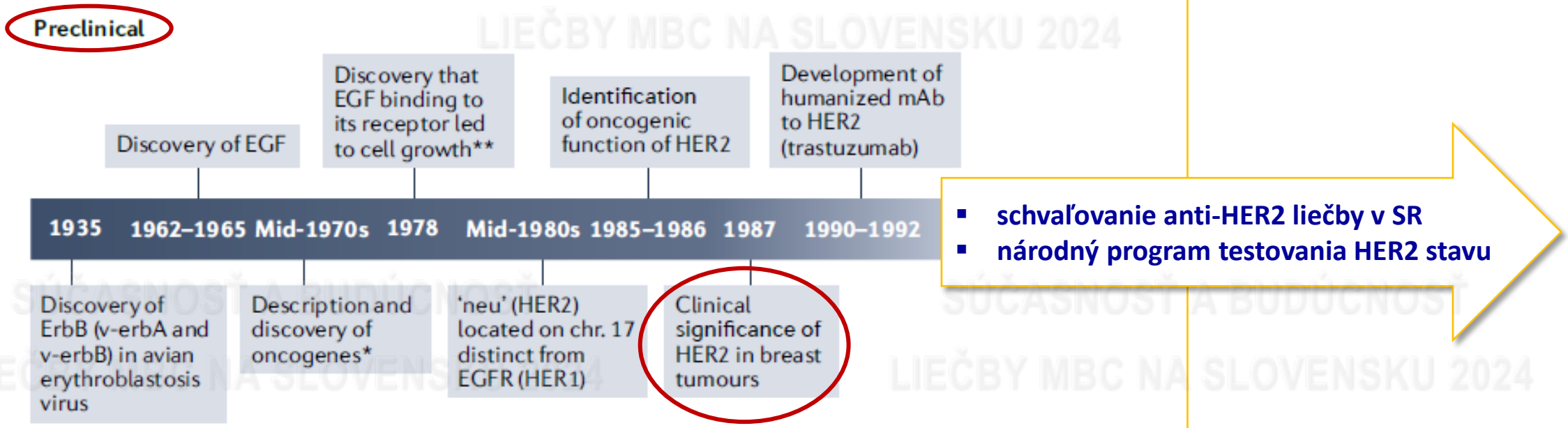
- **ER-pozit., HER2-negat.**
- **ER-pozit., HER2-pozit.**
- **ER-negat., HER2-pozit.**
- **ER-negat., HER2-negat.**

WHO classification of tumours series, 5th ed.; vol. 2).
Available from: https://tumourclassification.iarc.who.int/chapters/32.

Terapeutické využitie prediktívnej hodnoty nadmernej expresie/amplifikácie HER2



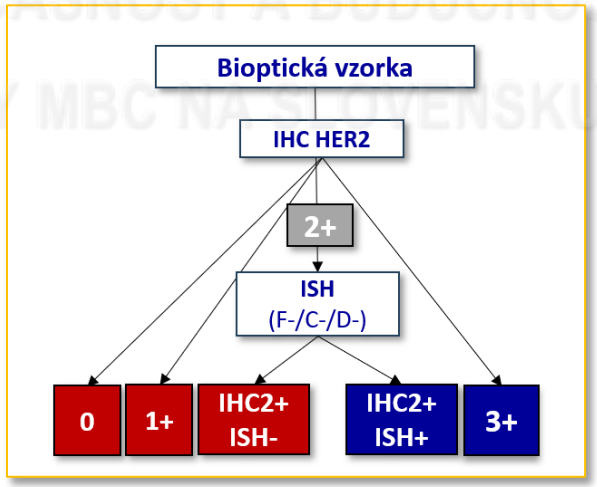
Hossain MS et al. Sensors | Volume 22 | no.19 | September 2022 | 7361

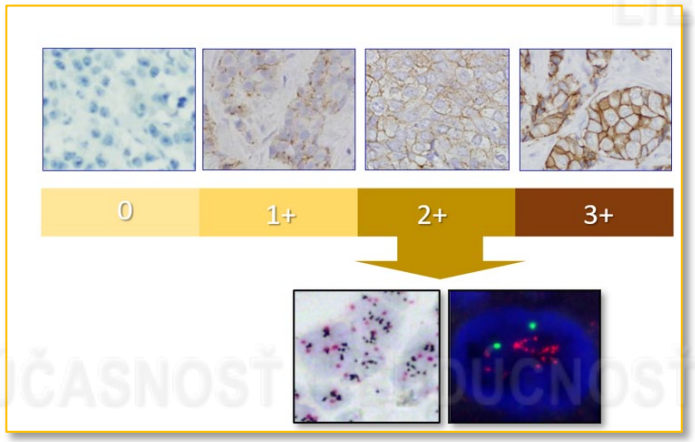


- schvaľovanie anti-HER2 liečby v SR
- národný program testovania HER2 stavu

Swain SM et al. Nature Reviews Drug Discovery | Volume 22 | February 2023 | 101–126

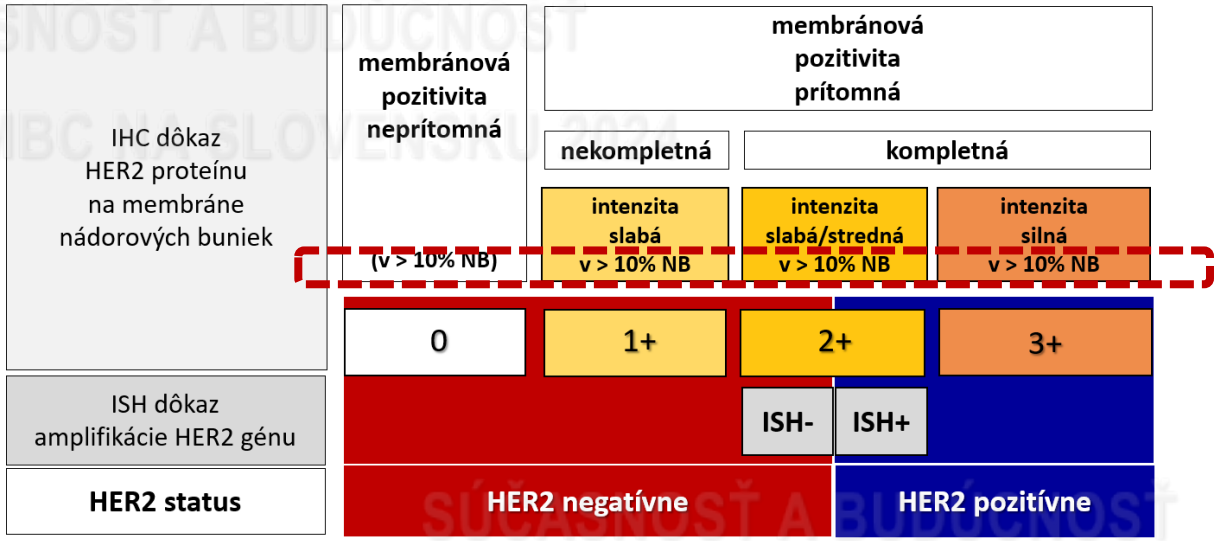
Štandardizované testovanie / hodnotenie „stavu HER2“ v SR od 2002-2003 doteraz





CAVE (!):

- MEMBRÁNOVÁ pozitivita
  - úplná al.
  - neúplná
- STUPEŇ (sila) POZITIVITY
- 10% všetkých TCs = „cut-off“
- VALIDOVANÉ ESEJE (IHC/ISH)
- IQA
- EQA



„HER2-pozitívne“ vs „ HER2-negatívne“ prípady podľa ASCO/CAP smerníc (Wolf AC et al. 2018 DOI: https://doi.org/10.1200/JOP.18.00206;)

Testovanie biomarkeru HER2 v SR podľa ESMO stav 2022-2023

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

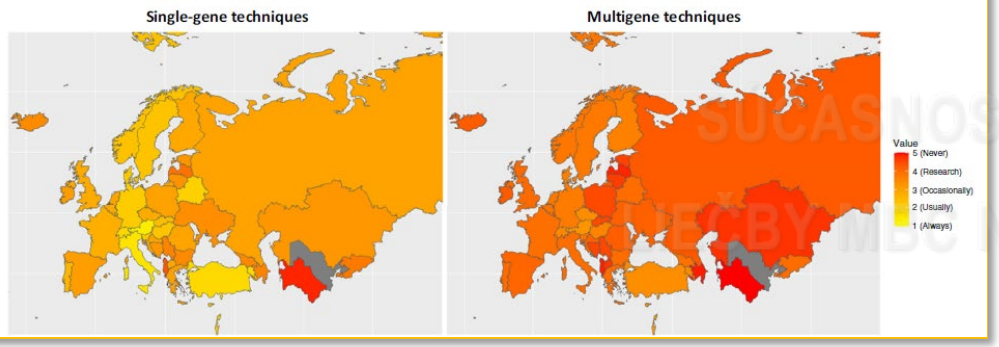
ANNALS OF ONCOLOGY driving innovation in oncology

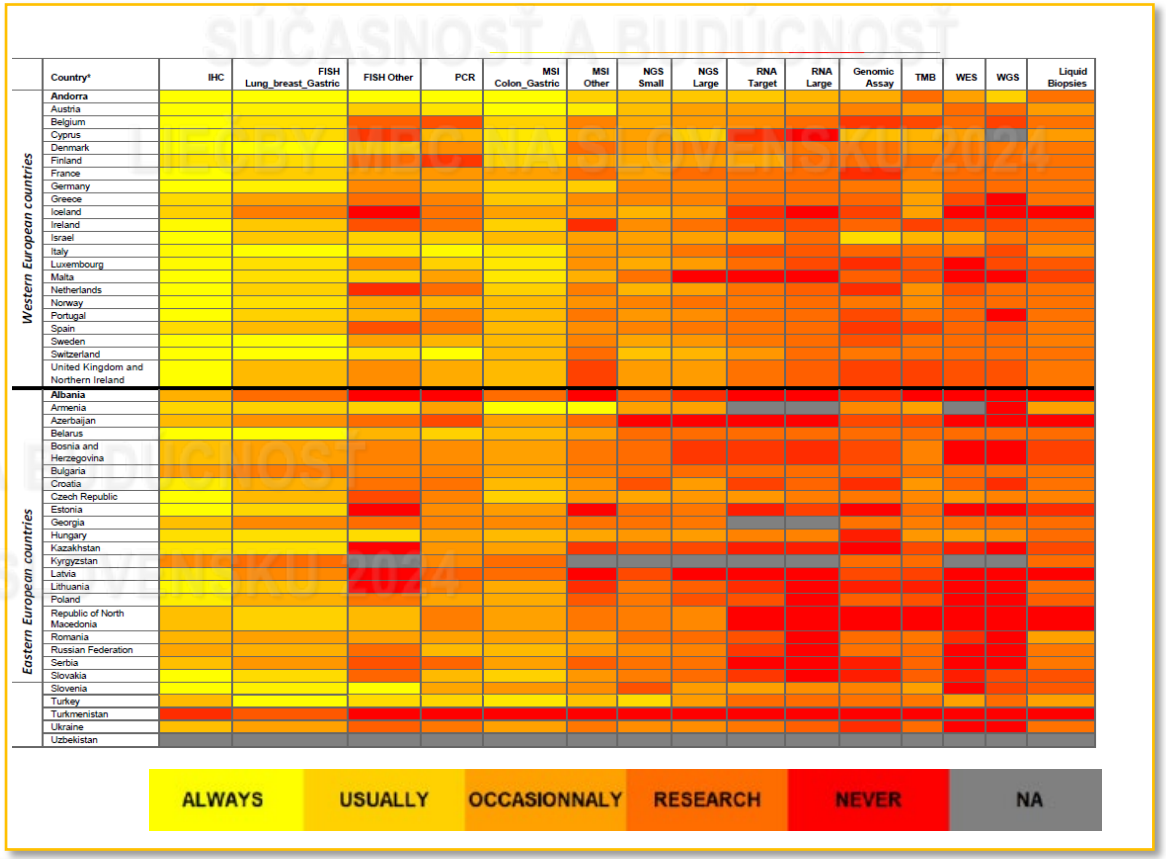
ORIGINAL ARTICLE

https://doi.org/10.1016/j.annonc.2023.06.011

ESMO study on the availability and accessibility of biomolecular technologies in oncology in Europe☆

A. Bayle[1,2,3,4,5*], J. Bonastre[3,4], D. Chaltiel[3,4], N. Latino[5], E. Rouleau[6,7], S. Peters[5,8], M. Galotti[5], G. Bricalli[5], B. Besse[2,9†] & R. Giuliani[5,10†]





Available online at www.sciencedirect.com

ScienceDirect

European Journal of Cancer 176 (2022) 70e77

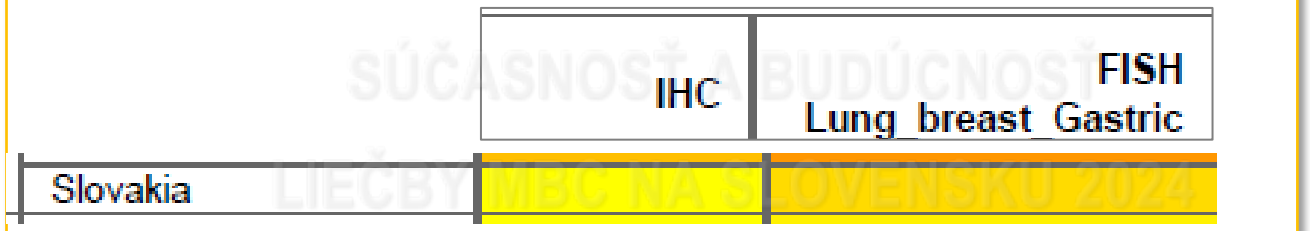
journal homepage: www.ejcancer.com

ELSEVIER

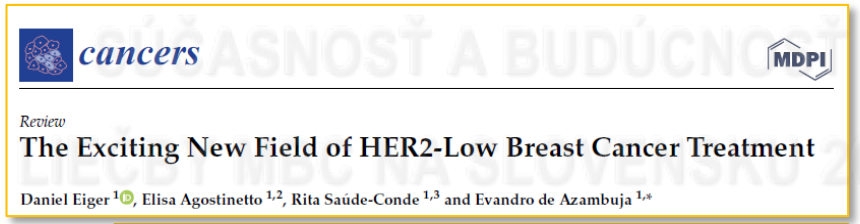
Original Research

Access and quality of biomarker testing for precision oncology in Europe

Nicola Normanno [a,*], Kathi Apostolidis [b], Audrey Wolf [c],



HER2 „low“ /„ultra-low: prediktívny faktor novej cielenej antiHER2-ADC-liečby

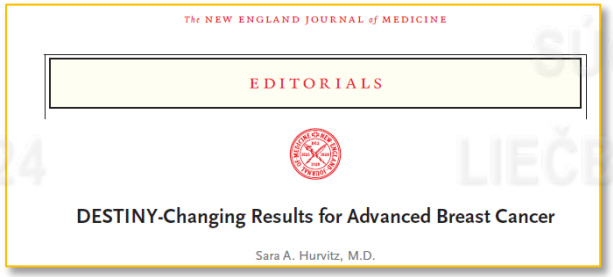

cancers

MDPI

Review

The Exciting New Field of HER2-Low Breast Cancer Treatment

Daniel Eiger [1], Elisa Agostinetto [1,2], Rita Saúde-Conde [1,3] and Evandro de Azambuja [1,*]


The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

DESTINY-Changing Results for Advanced Breast Cancer

Sara A. Hurvitz, M.D.


The Breast 67 (2023) 116–123

Contents lists available at ScienceDirect

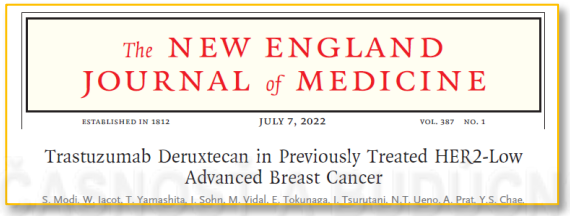
The Breast

journal homepage: www.journals.elsevier.com/the-breast

ELSEVIER

How I treat HER2-low advanced breast cancer

Ilana Schlam [a], Sara M. Tolaney [b], Paolo Tarantino [b,c,*]

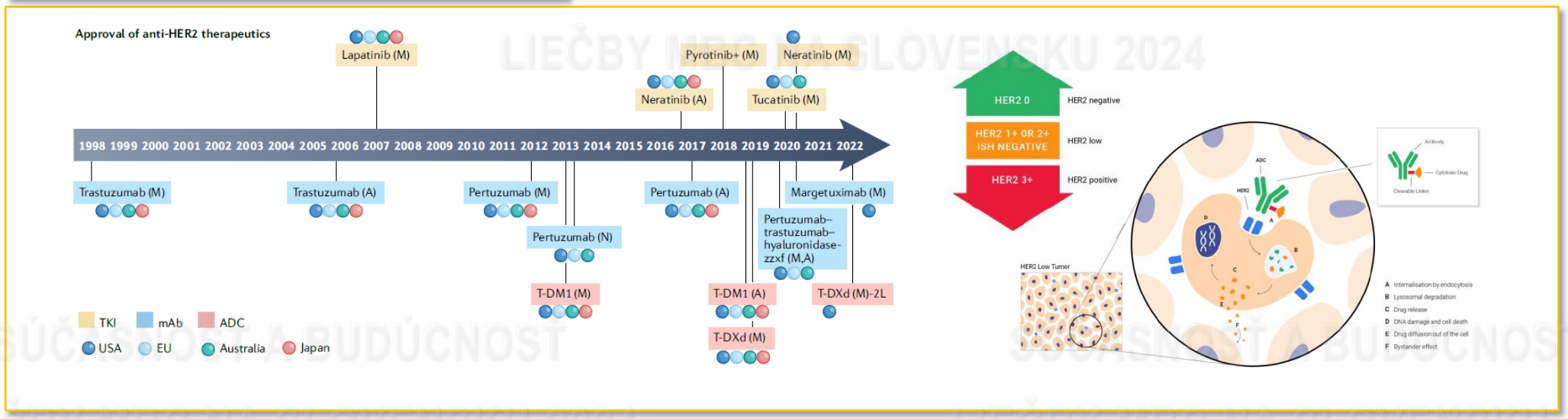

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae

- **Rôzne klinické štúdie,**
- **s rôznymi indikačnými kritériami liečby v štúdiách = „HER2-low“ / „ultra-low“**



Swain SM et al. Nature Reviews Drug Discovery | Volume 22 | February 2023 | 101–126, Popovic M et al. **2023**, 24, 8206. https://doi.org/10.3390/ijms24098206
Modi S et al. 2022, N Engl J Med 2022;387:9-20, Hurwitz SA N Engl J Med 387;1 nejm.org July 7, 2022, Schlamm I et al., 2023 The Breast 116-123
Eiger D, et al. Cancers **2021**, 13, 1015. Walko CM a West HJ. *JAMA Oncol.* 2019;5(11):1648

Nárast údajov o tzv. „low“ a aj „ultra-low“ pozitivite HER2

HER2-Low Breast Cancer: Pathological and Clinical Landscape

Paolo Tarantino, MD[1,2]; Erika Hamilton, MD[3]; Sara M. Tolaney, MD, MPH[4]; Javier Cortes, MD, PhD[5,6]; Stefania Morganti, MD[1,2]; Emanuela Ferraro, MD[1,2]; Antonio Marra, MD[1,2]; Giulia Viale, MD[1,2]; Dario Trapani, MD[1,2]; Fatima Cardoso, MD[7]; Frédérique Penault-Llorca, MD, PhD[8,9]; Giuseppe Viale, MD[1,2]; Fabrice Andrè, MD, PhD[10]; and Giuseppe Curigliano, MD, PhD[1,2]

Tarantino P et al., JCO 2022
DOI https://doi.org/10.1200/JCO.19.02488

frontiers in Molecular Biosciences

REVIEW
published: 15 March 2022
doi: 10.3389/fmolb.2022.834651

HER2 Low, Ultra-low, and Novel Complementary Biomarkers: Expanding the Spectrum of HER2 Positivity in Breast Cancer

Konstantinos Venetis[1,2†], Edoardo Crimini[2,3†], Elham Sajjadi[1,2], Chiara Corti[2,3],

Venetis K, et al. 2022 | Volume 9 | Article 834651

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

HER2-low expression in patients with advanced or metastatic solid tumors

B. Uzunparmak[1], C. Haymaker[2], G. Raso[2], S. Masciari[3], L. Wang[3], H. Lin[4], A. Gorur[1], B. Kirby[1], A.-M. Cimo[1], A. Kennon[1],

https://doi.org/10.1016/j.annonc.2023.08.005

cancers

Review

Current Biological, Pathological and Clinical Landscape of HER2-Low Breast Cancer

Huina Zhang [1,*] and Yan Peng [2,*]

Zhang H, Peng Y. Cancers 2023, 15, 126.

USCAP

www.nature.com/modpathol

ARTICLE

HER2-low breast cancers: incidence, HER2 staining patterns, clinicopathologic features, MammaPrint and BluePrint genomic profiles

Huina Zhang [1,3✉], Hani Katerji [1,3], Bradley M. Turner [1], William Audeh [2] and David G. Hicks [1✉]

Zhang H et al, Modern Pathology (2022) 35:1075–1082;

Comprehensive characterization of HER2-low breast cancers: implications in prognosis and treatment

Yuyang Li,[a,b] Julia Y. Tsang,[c] Fiona Tam,[d] Thomson Loong,[e] and Gary M. Tse[c,*]

Li Y et al., eBioMedicine 2023;91: 104571.

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 17 August 2023
DOI 10.3389/fonc.2023.1210314

Check for updates

OPEN ACCESS

EDITED BY
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Institut du Cancer de Montpellier (ICM), France

REVIEWED BY
Marzia Locatelli,
European Institute of Oncology (IEO), Italy
Sarbjeet Makkar,

HER-2 ultra-low breast cancer: exploring the clinicopathological features and prognosis in a retrospective study

Jiajie Shi, Liqiu Zhang and Cuizhi Geng*

Front. Oncol. 13:1210314.doi: 10.3389/fonc.2023.1210314

International Journal of Molecular Sciences

MDPI

Review

Low and Ultra-Low HER2 in Human Breast Cancer: An Effort to Define New Neoplastic Subtypes

Mariausilia Franchina [1], Cristina Pizzimenti [2], Vincenzo Fiorentino [1], Maurizio Martini [1], Giuseppina Rosaria Rita Ricciardi [3], Nicola Silvestris [1], Antonio Ieni [1] and Giovanni Tuccari [1,*]

Franchina M et al., Int. J. Mol. Sci. **2023**, 24, 12795.

Breast Cancer: Targets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

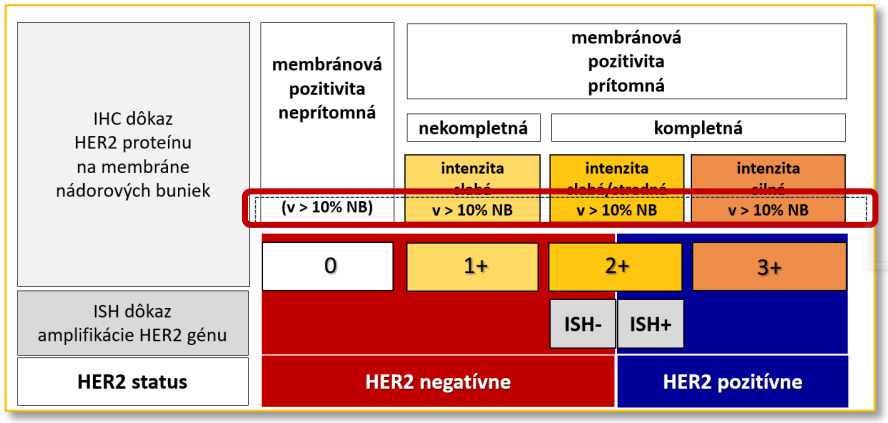
REVIEW

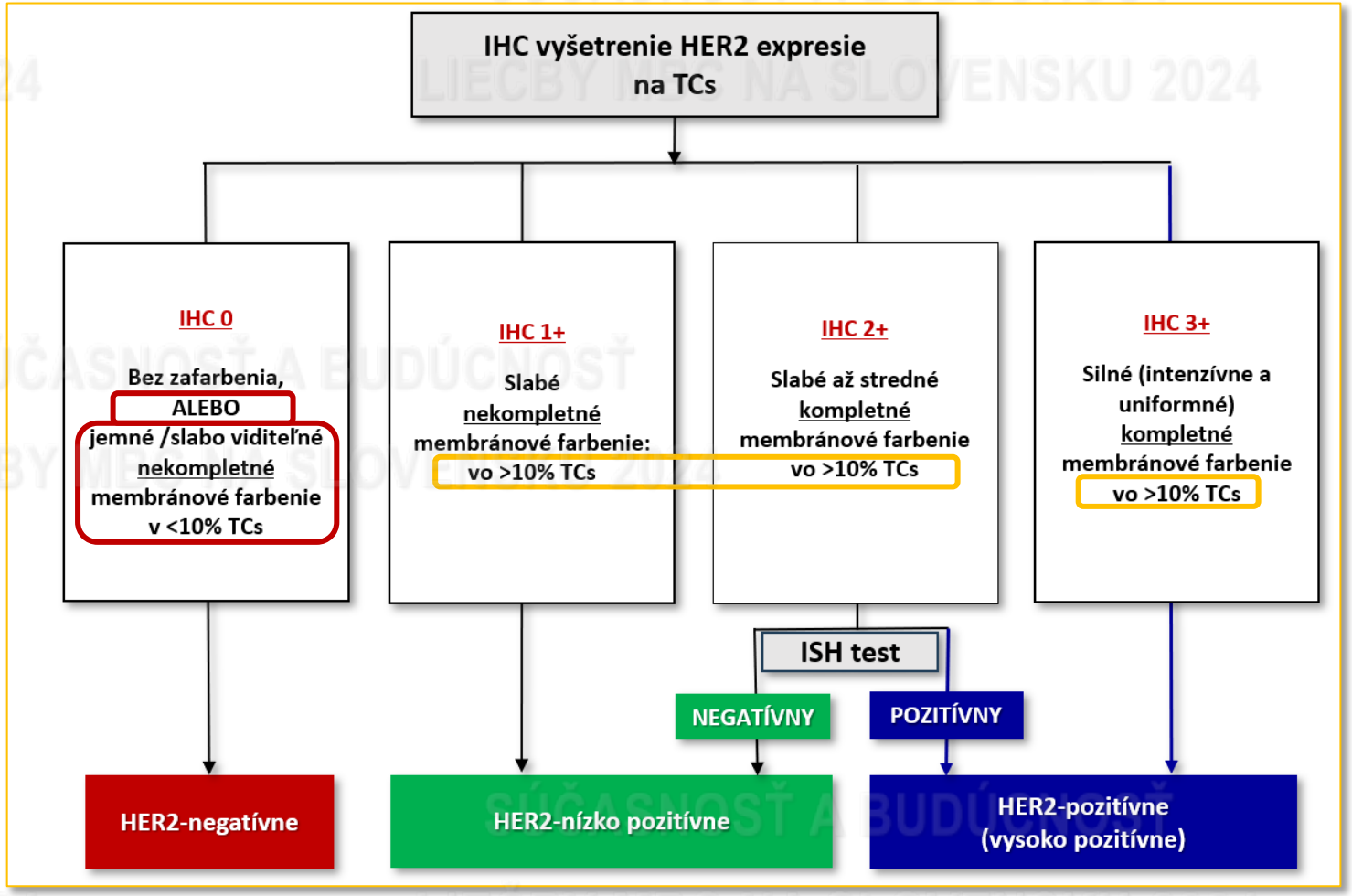
HER2-Low Breast Cancer: Current Landscape and Future Prospects

Yelena Shirman, Shlomit Lubovsky, Ayelet Shai

Breast Cancer: Targets and Therapy 2023:15 605–616

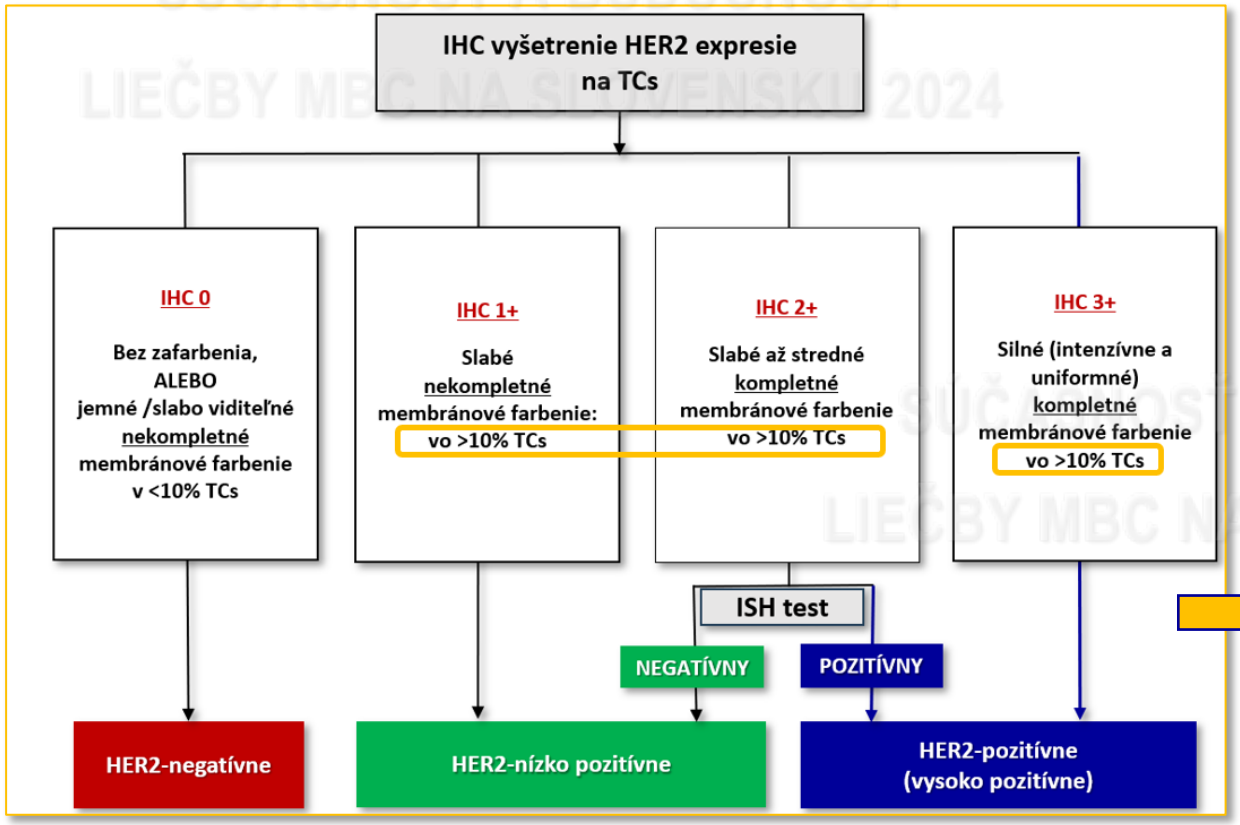
Testovanie „low“ a „ultra-low“ stavu HER2 v klin. štúdiách I.

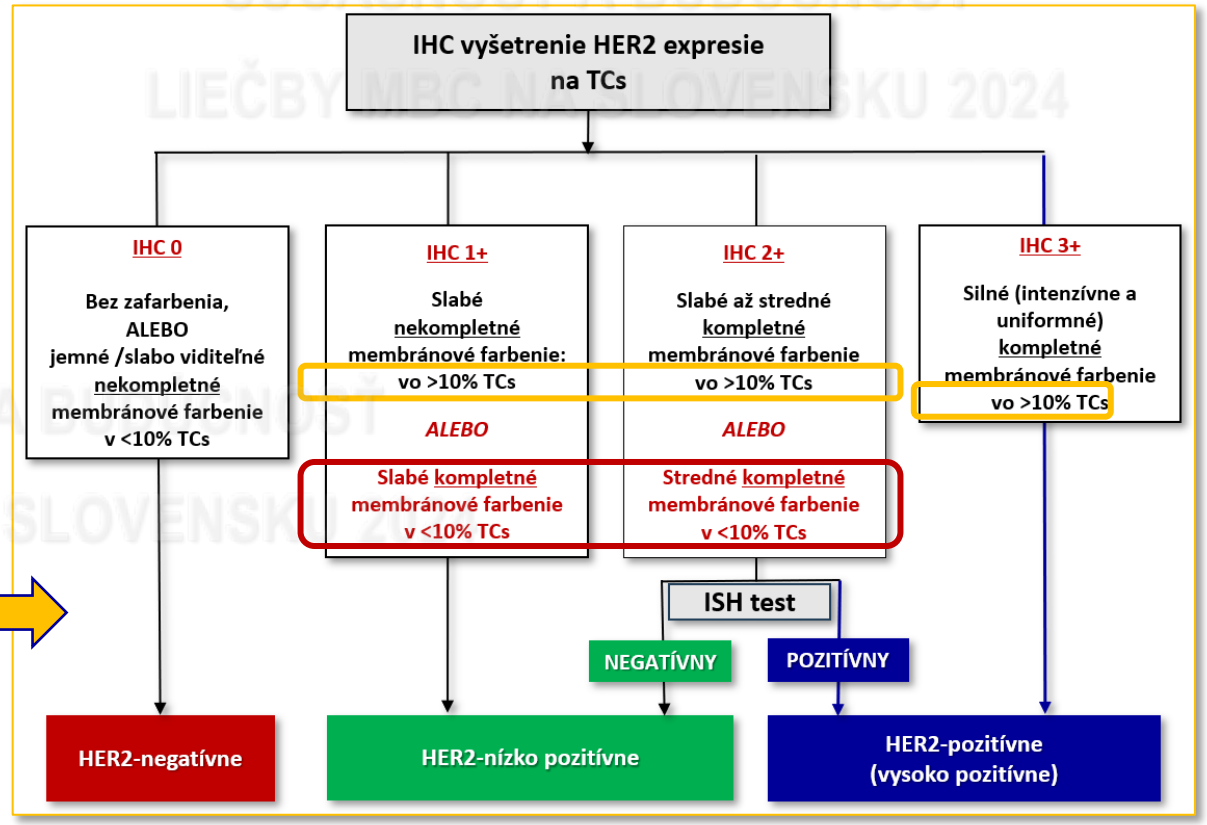




Upravené podľa Tarantino P et al., JCO 2022 DOI https://doi.org/10.1200/JCO.19.02488

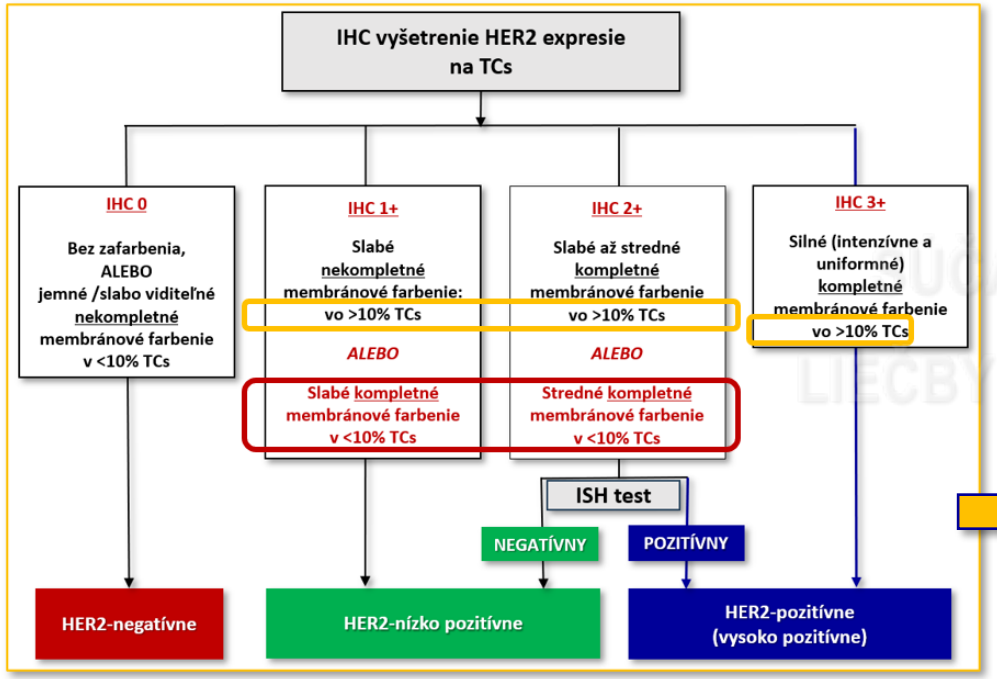
Testovanie „low“ a „ultra-low“ stavu HER2 v klin. štúdiách II.

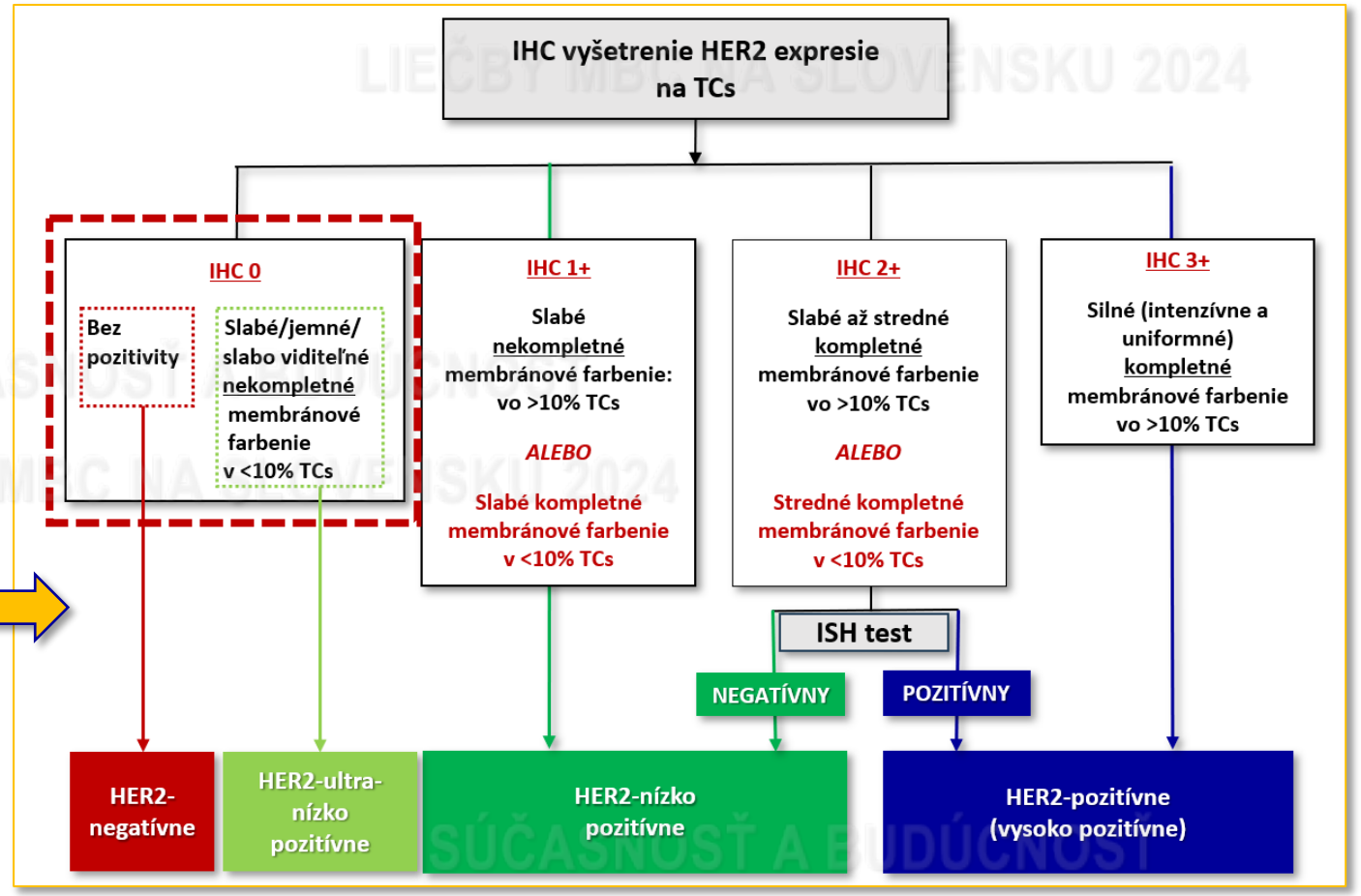




Upravené podľa Tarantino P et al., JCO 2022 DOI https://doi.org/10.1200/JCO.19.02488

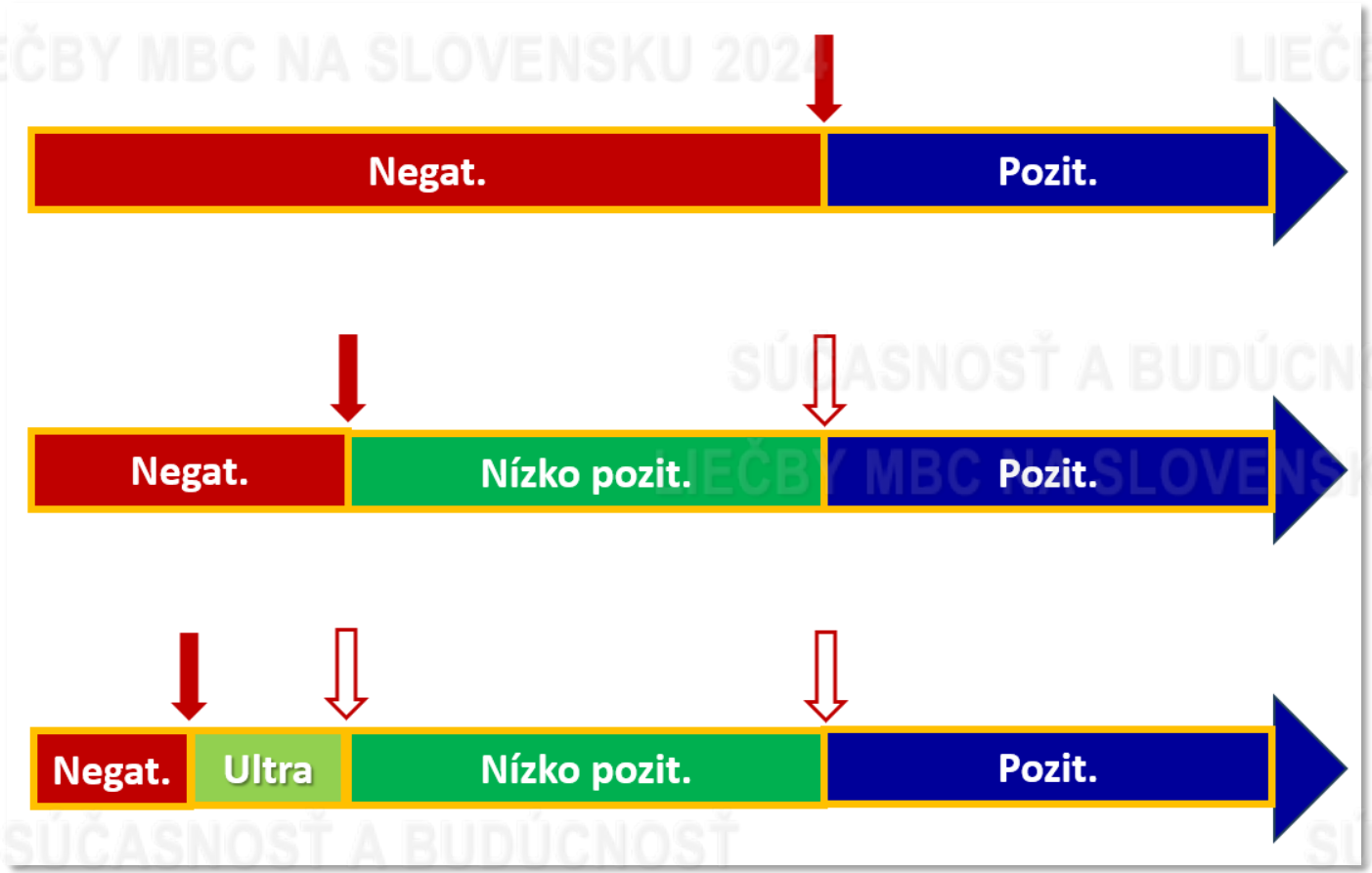
Testovanie „low“ a „ultra-low“ stavu HER2 v klin. štúdiách III.

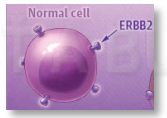


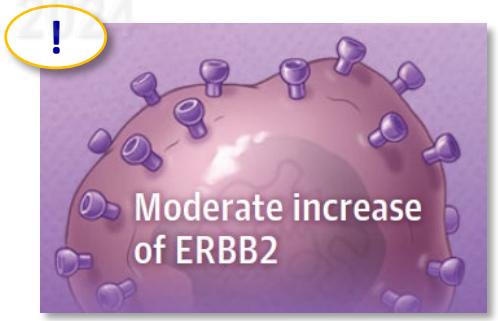


Kompilácia údajov podľa viacerých zdrojov:
Tarantino P et al., JCO 2022 DOI https://doi.org/10.1200/JCO.19.02488, https://www.aiforia.com/resource-library/how-can-ai-assist-in-detecting-her2-low-breast-cancer
Rakha EA et al. J Clin Pathol 2023;**76**:217–227, Wolf AC et al. DOI: https://doi.org/10.1200/JOP.18.00206

SÚHRN: Posuny „cut-off“ HER2 pozitivity v klin. štúdiách IV.







Aj iné metódy než „klasická kombinácia“ IHC + ISH ?

Kresba: Walko CM a West HJ. *JAMA Oncol.* 2019;5(11):1648.

Možnosti NGS a tekutých biopsií na dg. a monitoring „low“ a „ultra-low“ stavu HER2 (?)

Original Reports | Precision Medicine

Clinical Implication of *HER2* Aberration in Patients With Metastatic Cancer Using Next-Generation Sequencing: A Pan-Tumor Analysis

Jun J et al., 2023 JCO Precis Oncol 7:e2200537

- ... **a great majority of patients** with HER2 amplification and/or HER2 fusion had **HER2 + tumor by IHC**.

Pathology
Volume 56, Issue 3, April 2024, Pages 325-333

ANATOMICAL PATHOLOGY

Comparison of an amplicon-based large panel next generation sequencing (NGS) assay with conventional testing methods for *MET* and *HER2* amplification in lung and breast cancers

Tay TKY et al., 2024
https://doi.org/10.1016/j.pathol.2023.10.011

- In summary, the NGS assay has good concordance with conventional testing methods but **may be less sensitive in detecting low level** gene amplification.

3061 Poster Session

Liquid biopsy identification of ERBB2 amplified and HER2 expressing metastatic breast cancer: Comparison and combination of cell and cell-free platforms.

Giuseppe Di Caro, Ernest Lam, David Bourdon, Tatjana Singer, Kandra Horne, Megan Slade, Rick Wenstrup, Lee S. Schwartzberg; Epic Sciences, San Diego, CA; Epic Sciences, La Jolla, CA; Renown Health, Reno, NV

Giordani et al. J Exp Clin Cancer Res (2024) 43:182
https://doi.org/10.1186/s13046-024-03105-9

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Monitoring changing patterns in HER2 addiction by liquid biopsy in advanced breast cancer patients

Giordani et al. J Exp Clin Cancer Res (2024) 43:182

1. **CTCs**
2. **alterations in plasma ctDNA.**

Ale ide aj o požiadavky bioinformatiky...

editorials

Ferrying Oncologists Across the Chasm of Interpreting Biomarker Testing Reports: Systematic Support Needed to Improve Care and Decrease Disparities

Howard (Jack) West, MD[1] and Christine M. Lovly, MD, PhD[2]

JCO Clin Practice DOI https://doi.org/10.1200/OP.23.00010

of molecular diagnostics companies. For example, just as ASCO/AMP/CAP has developed joint guidelines for interpretation and reporting of sequence variants, it would be helpful for these professional societies to produce consensus guidelines on the content and language of the reports to maximize interpretability by clinicians.

would translate these results into management decisions. To be able to serve the volume-based needs of the oncology community, molecular consult services would ideally perform asynchronous reviews to generate reports on an ongoing basis. Moreover, it would be beneficial to have their expertise available in real time, on demand. Such support would entail

ascribed mechanism of action, a robust AI-supported strategy could potentially be developed to provide a clearly articulated and prioritized set of clinical suggestions for direct application by the recipient clinician(s). Such a synthesis of human-

Ale ide aj o podporu AI

RESEARCH

HAHNet: A convolutional neural network for HER2 status classification of breast cancer

Jiahao Wang[1,2], Xiaodong Zhu[1,2,3], Kai Chen[1,2], Lei Hao[1,2] and Yuanning Liu[1,2,3*]

https://doi.org/10.21203/rs.3.rs-2841300/v1

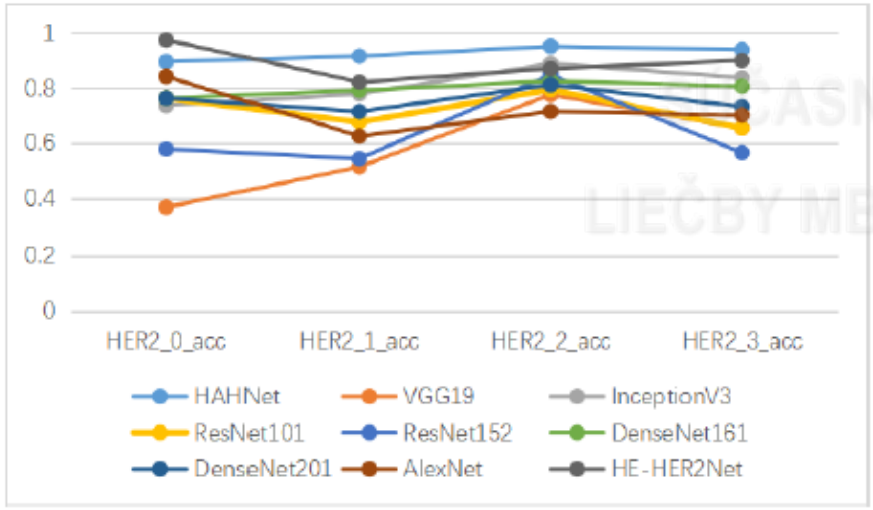


Figure 8 Comparison of the accuracy of different methods for predicting HER2 status

Ale ide aj o podporu AI

RESEARCH

HAHNet: A convolutional neural network for HER2 status classification of breast cancer

Jiahao Wang[1,2], Xiaodong Zhu[1,2,3], Kai Chen[1,2], Lei Hao[1,2] and Yuanning Liu[1,2,3*]

https://doi.org/10.21203/rs.3.rs-2841300/v1

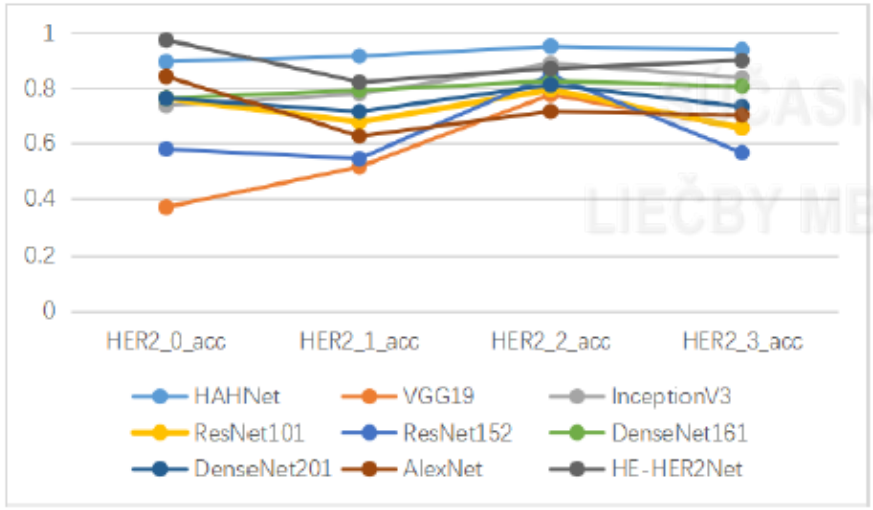


Figure 8 Comparison of the accuracy of different methods for predicting HER2 status

MDPI

Data Descriptor

Dataset of Hematoxylin-eosin and Ki67 histopathological image pairs complemented by algorithms providing Ki67 index

Dominika Petríková [1,*], Ivan Cimrák [1], Katarína Tobiášová [2], Lukáš Plank [2]

https://doi.org/10.5281/zenodo.11218961

Financované Európskou úniou NextGenerationEU

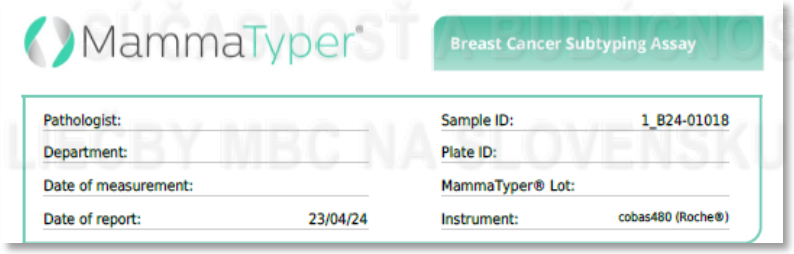
MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY

PLÁN OBNOVY

Výzva na predkladanie žiadostí o poskytnutie prostriedkov mechanizmu na podporu obnovy a odolnosti

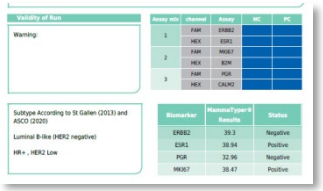
Základné údaje	
Vykonávateľ:	Ministerstvo zdravotníctva Slovenskej republiky
Názov výzvy:	„Digitalizovaná patológia podporovaná umelou inteligenciou“
Kód výzvy:	11I03-21-V19

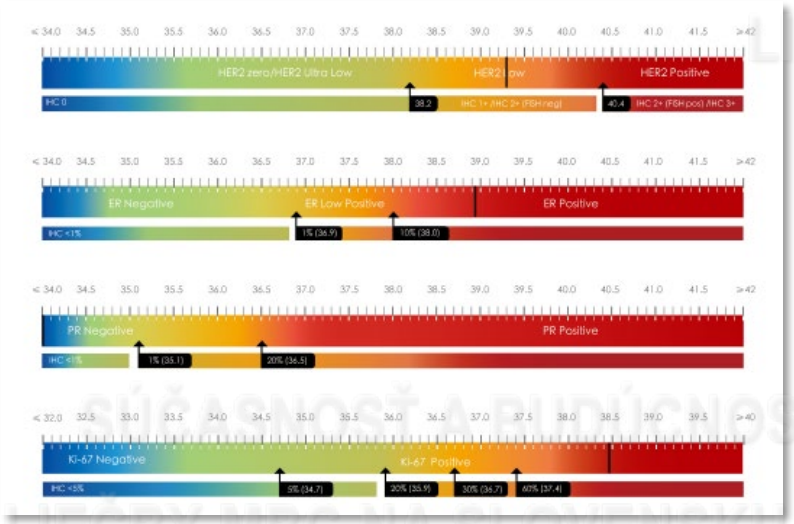
MammaTyper® www.cercabiotech.com


MammaTyper®

Breast Cancer Subtyping Assay

Pathologist:
Department:
Date of measurement:
Date of report: 23/04/24
Sample ID: 1_B24-01018
Plate ID:
MammaTyper® Lot:
Instrument: cobas480 (Roche®)





Validity of Run

Warning:

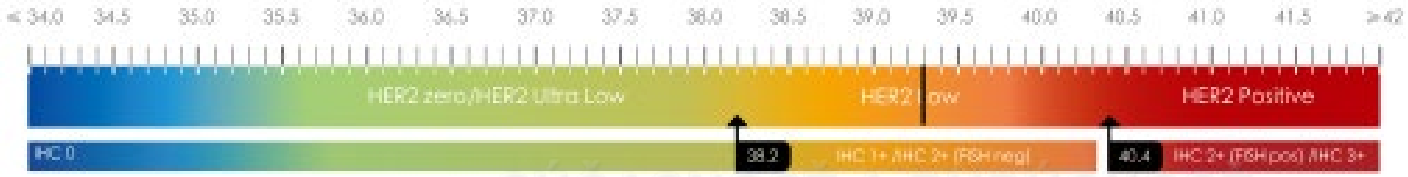
Assay mix	channel	Assay	NC	PC
1	FAM	ERBB2		
	HEX	ESR1		
2	FAM	MKI67		
	HEX	B2M		
3	FAM	PGR		
	HEX	CALM2		

Subtype According to St Gallen (2013) and ASCO (2020)

Luminal B-like (HER2 negative)

HR+ , HER2 Low

Biomarker	MammaTyper® Results	Status
ERBB2	39.3	Negative
ESR1	38.94	Positive
PGR	32.96	Negative
MKI67	38.47	Positive



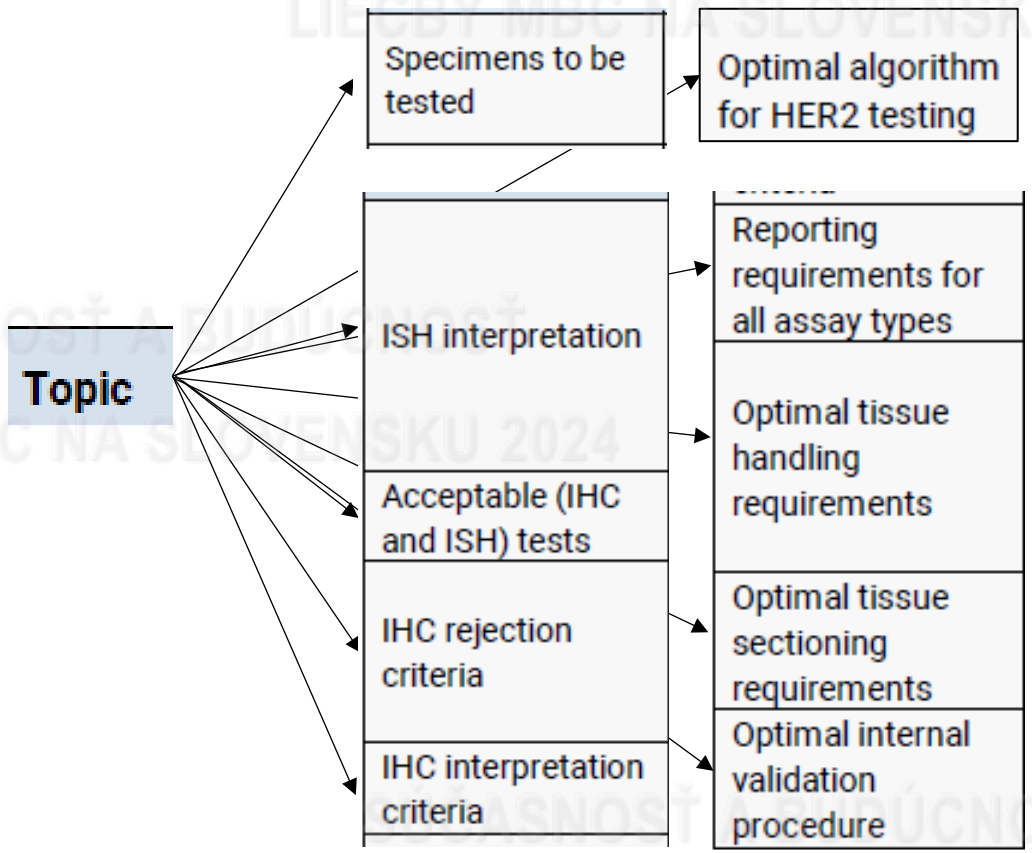
- RNA extrakcia z FFPE, qRT-PCR,
- kvantifikácia expresie HER2, ER, PR a Ki-67 mRNA,
- MammaTyper® Report Generator Software

Ako ďalej v klinickej „reálnej“ praxi: Návod pre patológov podľa ASCO/CAP (2023)

ASCO Guidelines

COLLEGE of AMERICAN PATHOLOGISTS

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-CAP Guideline Update				
Topic	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
The recommendations in previous (2013 and 2018) ASCO-CAP HER2 testing guideline updates are affirmed.				
Specimens to be tested	All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available.	-	-	-
Optimal algorithm for HER2 testing	IHC 2+ (equivocal) is invasive breast cancer with weak to moderate complete membrane staining observed in >10% of tumor cells.	EB	H	S
	On the basis of some criteria (including a tumor grade 3), if the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen.	EB	H	S
	If a case has a HER2/CEP17 ratio is ≥2.0 but the average *HER2* signals/cell is <4.0, a definitive diagnosis will be rendered based on additional workup. If not already assessed by the institution/laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH and the slides from both ISH and IHC be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment): **a.** If the IHC result is 3+, diagnosis is HER2 positive. **b.** If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that includes the area of invasive cancer with IHC 2+ staining: - If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category. - If the count remains an average of <4.0 *HER2* signals/cell and *HER2*/CEP17 ratio ≥2.0, the diagnosis is HER2 negative with a comment.[a] **c.** If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment. [a]	EB	I	S
	If a case has an average of ≥6.0 *HER2* signals/cell with a *HER2*/CEP17 ratio of <2.0, formerly diagnosed as ISH positive for HER2, a definitive diagnosis will be rendered based on additional workup. If not already assessed by the institution/lab performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH and the slides from both ISH and	EB	I	S

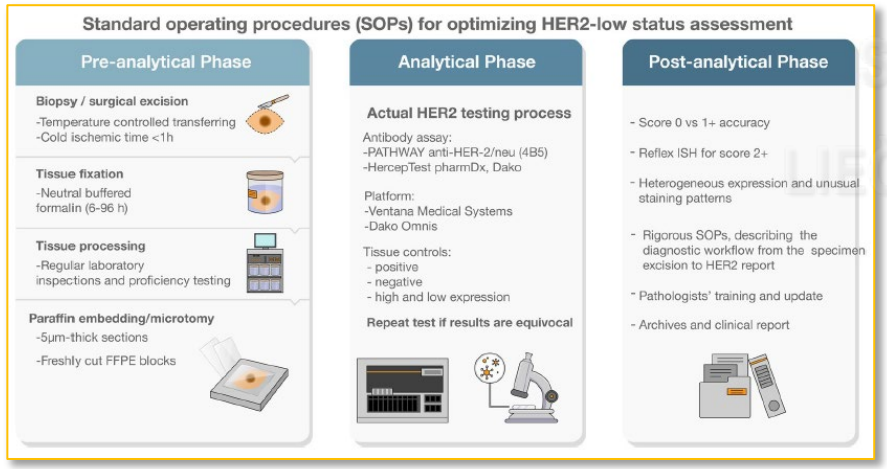


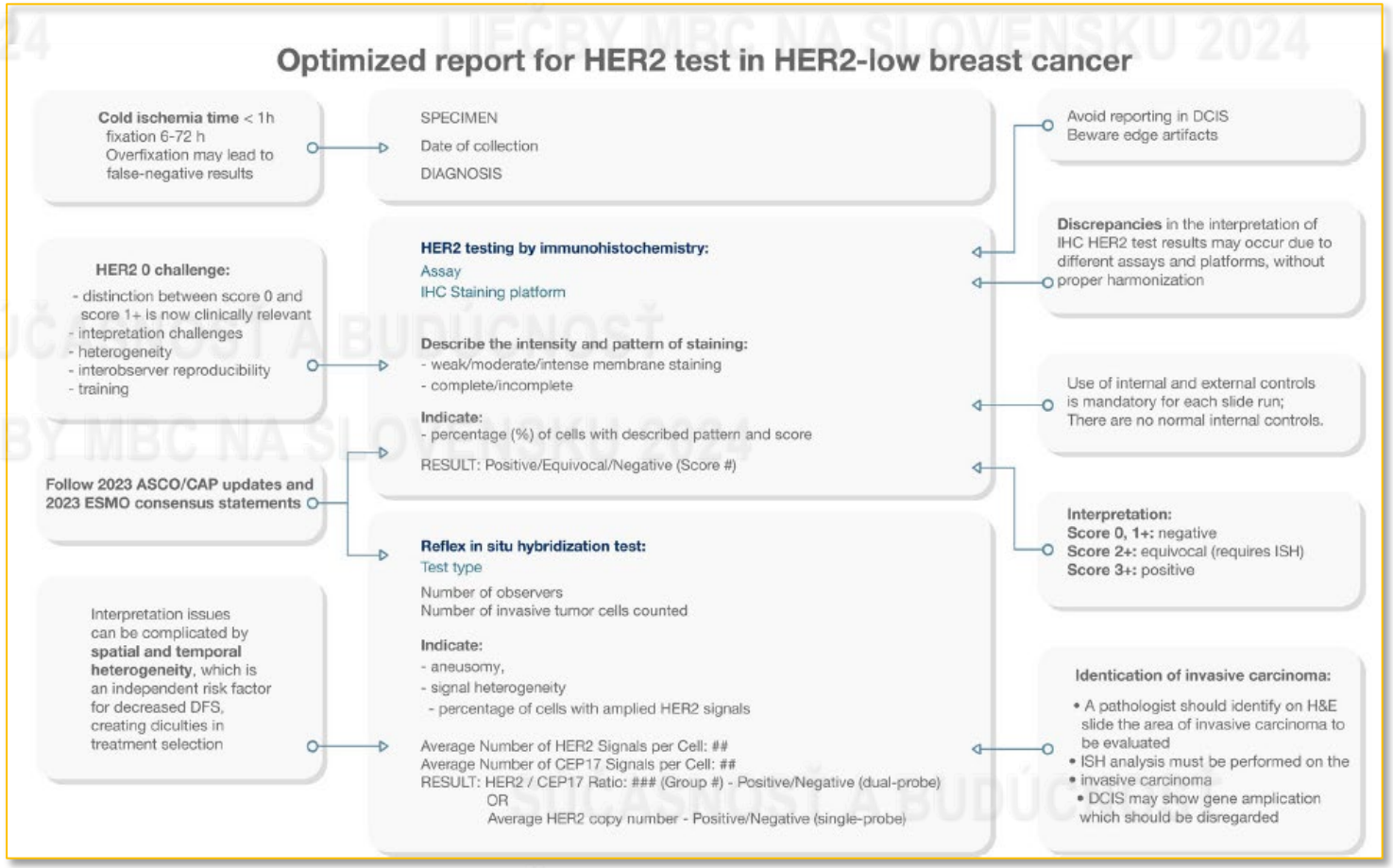
www.asco.org/breast-cancer-guidelines

Ako ďalej v klinickej „reálnej“ praxi: Návod pre patológov podľa ASCO/CAP (2023)

REVIEW AND PERSPECTIVES

Standardized pathology report for HER2 testing in compliance with 2023 ASCO/CAP updates and 2023 ESMO consensus statements on HER2-low breast cancer





Ivanova M et al., Virchows Arch (2024) 484:3-14, https://doi.org/10.1007/s00428-023-03656-w

Ako ďalej v klinickej „reálnej“ praxi: smernice ESMO, ASCO/CAP, UK (2023)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer

Tarantino et al., **2023** https://doi.org/10.1016/j.annonc.2023.05.008

➢ ESMO:

Table 1. Interpretation by the ASCO/CAP 2018 Guidelines and by the 2023 ESMO Consensus on HER2-low breast cancer regarding each pattern of HER2 staining

Description of staining	Denomination by 2018 ASCO/CAP Guidelines	Conclusion by 2018 ASCO/CAP Guidelines	Conclusion by 2023 ESMO clinical practice recommendations
- No staining	HER2-0	HER2-negative	**HER2-0** *HER2-null*[a]
- Incomplete or faint staining in ≤10% of invasive tumor cells	HER2-0	HER2-negative	*HER2-ultralow (or >no staining <1+)*[a]
- Incomplete or faint staining in >10% of invasive tumor cells	HER2 1+	HER2-negative	**HER2-low**
- Weak to moderate complete membrane staining in >10% of invasive tumor cells (ISH-negative)	HER2 2+ nonamplified	HER2-negative	**HER2-low**
- Weak to moderate complete membrane staining in >10% of invasive tumor cells (ISH-positive)	HER2 2+ amplified	HER2-positive	**HER2-positive**
- Intense complete membrane staining in >10% of invasive tumor cells	HER2 3+	HER2-positive	**HER2-positive**

Ako ďalej v klinickej „reálnej“ praxi: smernice ESMO, ASCO/CAP, UK (2023)

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- Incomplete or faint staining in >10% of invasive tumor cells	HER2 1+	HER2-negative	HER2-low
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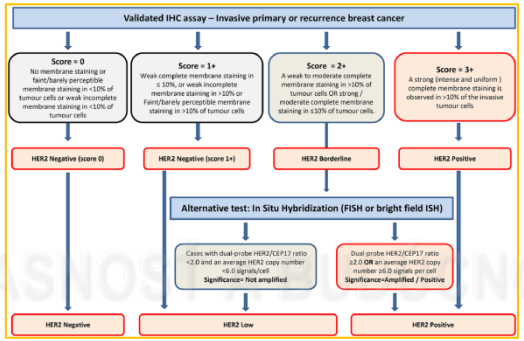
UK recommendations for HER2 assessment in breast cancer: an update

Rakha EA, Tan PH, Quinn C, et al. J Clin Pathol 2023;**76**:217–227.

➢ UK



Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update

Wolff AC et al. J Clin Oncol 41:3867-3872 © 2023 by ASCO-CAP

➢ ASCO/CAP:

- **HER2 testing guidelines 2018** have focused on identifying **HER2 protein overexpression or gene amplification** in breast cancer **to identify patients for therapies that disrupt HER2 signaling.**

This update acknowledges a new indication for TDX **when HER2** is not overexpressed or amplified but **is IHC 1+ or 2+ without amplification**

- Therefore, while it is **premature to create new result categories of HER2 expression** (eg, HER2-Low, HER2-Ultra-Low), **best practices to distinguish IHC 0 from 1+** are now **clinically relevant.**

Ako ďalej v klinickej „reálnej“ praxi: smernice ESMO, ASCO/CAP, UK (2023)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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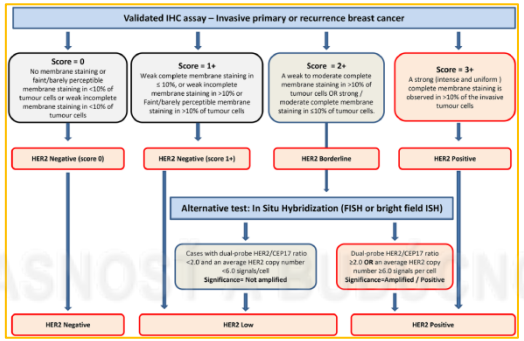

- **It is important to note that HER2- low does not denote a novel BC subtype but rather serves as a descriptive diagnostic category.**
- **However, pathologists are now tasked with specifically identifying the intricate subtleties of HER2 expression dynamics across a wider continuum, an aspect that was previously deemed clinically irrelevant.**

Ivanova M et al., https://doi.org/10.1007/s00428-023-03656-w

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update

Wolff AC et al. J Clin Oncol 41:3867-3872 © 2023 by ASCO-CAP

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  This update acknowledges a new indication for TDX **when HER2** is not overexpressed or amplified but **is IHC 1+ or 2+ without amplification**
- Therefore, while it is **premature to create new result categories of HER2 expression** (eg, HER2-Low, HER2-Ultra-Low), **best practices to distinguish IHC 0 from 1+** are now **clinically relevant.**

Ako ďalej v našej klinickej „reálnej“ praxi:

Novinky v testovaní stavu HER2 v biopsiách pacientov s karcinómom prsnej žľazy

Prof. MUDr. Lukáš Plank, CSc.[1, 2]
[1]Ústav patologickej anatómie Jesseniovej lekárskej fakulty Univerzity Komenského a Univerzitnej nemocnice v Martine
[2]Martinské bioptické centrum, s. r. o., Martin

Prehľadový článok, ktorý sumarizuje požadavky na testovanie stavu HER2 v bioptických vzorkách pacientov s karcinómom prsnej žľazy, keďže identifikácia HER2 pozitívneho stavu je tradičným prediktívnym biomarkerom anti-HER2 liečby. HER2 negatívnemu stavu sa venovala menšia pozornosť, ale v súvislosti s novými terapeutickými modalitami publikovanými v klinických štúdiách vyžaduje precízne zhodnotenie každého HER2 stavu. Preto sa v článku venuje pozornosť detailom analýzy stavu HER2 kombináciou imunohistochemickej a *in situ* hybridizačnej metódy, ako aj zhodnotenia analýzy v zmysle skóre 0-3+ vrátane tzv. nízkej a ultranízkej expresie HER2 proteínu. Súčasne sa v kontexte recentných smerníc odporúča zachovať doterajší spôsob hodnotenia stavu HER2 s detailnou deskripciou expresie HER2 proteínu, resp. výsledku analýzy amplifikácie *HER2* génu. Doterajšia úroveň poznatkov nepodporuje implementáciu nových kategórií nízkej a ultranízkej expresie HER2 do bioptického záveru patológa, aj keď v klinickej onkológii predstavujú požiadavku na indikáciu nových liečebných modalít.

Kľúčové slová: karcinóm prsnej žľazy, HER2 status pozitívny a negatívny, nízka a ultranízka expresia HER2 proteínu

New approaches in the testing of HER2 status in the biopsies of breast carcinoma patients

The identification of HER2 positivity represents a traditional predictive biomarker for anti-HER2 therapy. In this review article we summarize new requirements on HER2 testing of biopsy specimen of breast cancer patients, Although previously less attention has been paid to HER2 negativity, the new theraeutical modalities published in some clinical studies highlight the importance of a precise HER2 evaluation of all breast cancers. In this article the attention has been paid to the detailed description of the HER2 analyses using a combination of the imunohistochemical and *in situ* hybridization methods, as well as to the precise evaluation and reporting of the HER score from 0 to 3+, incl. descriptions of the so-called HER low and HER2-ultra-low cancers. However, in agreement with recent guidelines the pathologists should continue to use the traditional evaluation of individual HER2 categories with inclusion of a detailed data on the HER2 protein expression and on the *HER2* gene status resp. Contemporary level of knowledge does not support to implement the HER2-low and HER2-ultra-low categories as separate biological categories into the final biopsy report, although in clinical oncology their identification is required for the new therapeutical modalities.

Key words: breast cancer, HER2: positivity and negativity, low and ultra-low HER2 expression

Onkológia (Bratisl.), 2024;19(2):115-119

Výsledok IHC analýzy HER2 expresie – 5 možností:

A/ Pozitívny stav – nadmerná expresia HER2 proteínu (3+) :
(silná, kompletná membránová expresia v > 10 % TCs)

B/ Nejednoznačný stav expresie HER2 proteínu (2+) :
(stredná/slabá kompletná membránová expresia v > 10 % TCs)
ISH vyšetrenie: bez amplifikácie vs amplifikácia HER2 génu

C/ Negatívny stav – bez nadmernej expresie HER2 proteínu (1+) :
(slabá a nekompletná /neúplná membránová expresia v > 10 % TCs)

D/ Negatívny stav – bez nadmernej expresie HER2 proteínu (0)
D.1. úplná absencia membránovej expresie v TCs
D.2. slabá a nekompletná membránová expresia v < 10% TCs

Pozn.: hodnotenie expresie výlučne v nádorových bunkách invazívnej komponenty (TCs)

Reprodukovateľnosť výsledkov a otázka retestovania po neoadjuvancii

Mod Pathol 37 (2024) 100535

MODERN PATHOLOGY

USCAP UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY Creating a Better Pathologist

Journal homepage: https://modernpathology.org/

Research Article

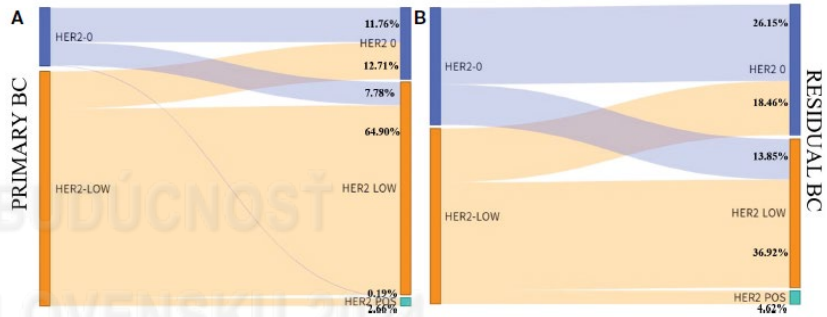
Development and Validation of a HER2-Low Focused Immunohistochemical Scoring System With High-Interobserver Concordance: The Australian HER2-Low Breast Cancer Concordance Study

Farshid G et al. 2024 https://doi.org/10.1016/j.modpat.2024.100535

- **reference set of cases with expert consensus HER2 scores** will be invaluable **for peer training**
- Pathologists **applying clear, explicit guidelines**, specifically focused on breast cancers with HER2 IHC expression **levels at the lower end of the spectrum**, can achieve **satisfactory levels of scoring accuracy and consistency**.

Evolution and clinical significance of HER2-low status after neoadjuvant therapy for breast cancer

Shang J et al. et al. Front. Oncol. 2023
doi: 10.3389/fonc.2023.1086480



cancers

MDPI

Review

Current Biological, Pathological and Clinical Landscape of HER2-Low Breast Cancer

Zhang H a Peng Y, Cancers 2023, 15, 126.

- **Shang et al. + Zhang a Peng:**

- HER2-low breast cancer is **highly unstable during disease evolution and progression...**

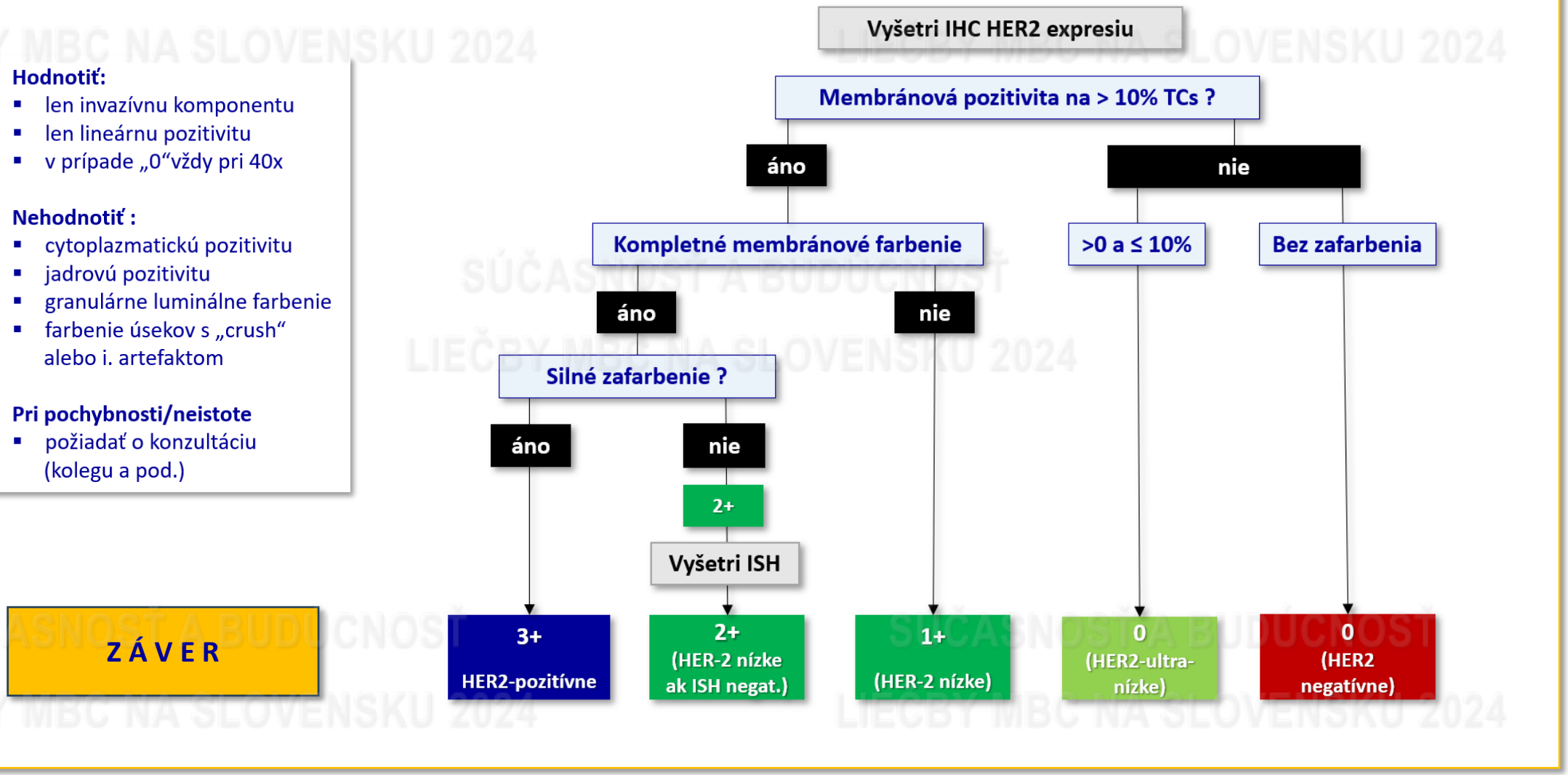
- Re-detection of HER2 in breast cancer **after neoadjuvant therapy** may lead to **new treatment opportunities** ...
for a **proportion of patients because of enrichment of HER2-low carcinomas in the advanced setting.** .

Návrh gradualistického postupu zhodnotenia stavu HER2

Hodnotiť:
- len invazívnu komponentu
- len lineárnu pozitivitu
- v prípade „0“vždy pri 40x

Nehodnotiť :
- cytoplazmatickú pozitivitu
- jadrovú pozitivitu
- granulárne luminálne farbenie
- farbenie úsekov s „crush“ alebo i. artefaktom

Pri pochybnosti/neistote
- požiadať o konzultáciu (kolegu a pod.)



Úprava podľa Farshid G et al. 2024, https://doi.org/10.1016/j.modpat.2024.100535

Miesto záveru ...

ASCO Daily News

Clinical News From the American Society of Clinical Oncology

TOPICS PODCASTS VIDEO ABOUT Enter words / phrases / DOI / ISBN / keywords / authors / etc

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Is HER2-Low a Unique Breast Cancer Subtype?

March 21, 2024

Concluding Remarks

The retrospective data available to address the question of whether HER2-low is a unique breast cancer subtype should be revisited prospectively with more accurate quantitative assays of HER2 expression before definitive conclusions can be drawn about the prognostic significance of HER2-low levels.

https://dailynews.ascopubs.org/do/her2-low-unique-breast-cancer-subtype