Quali test per la decisione terapeutica nel 2024?

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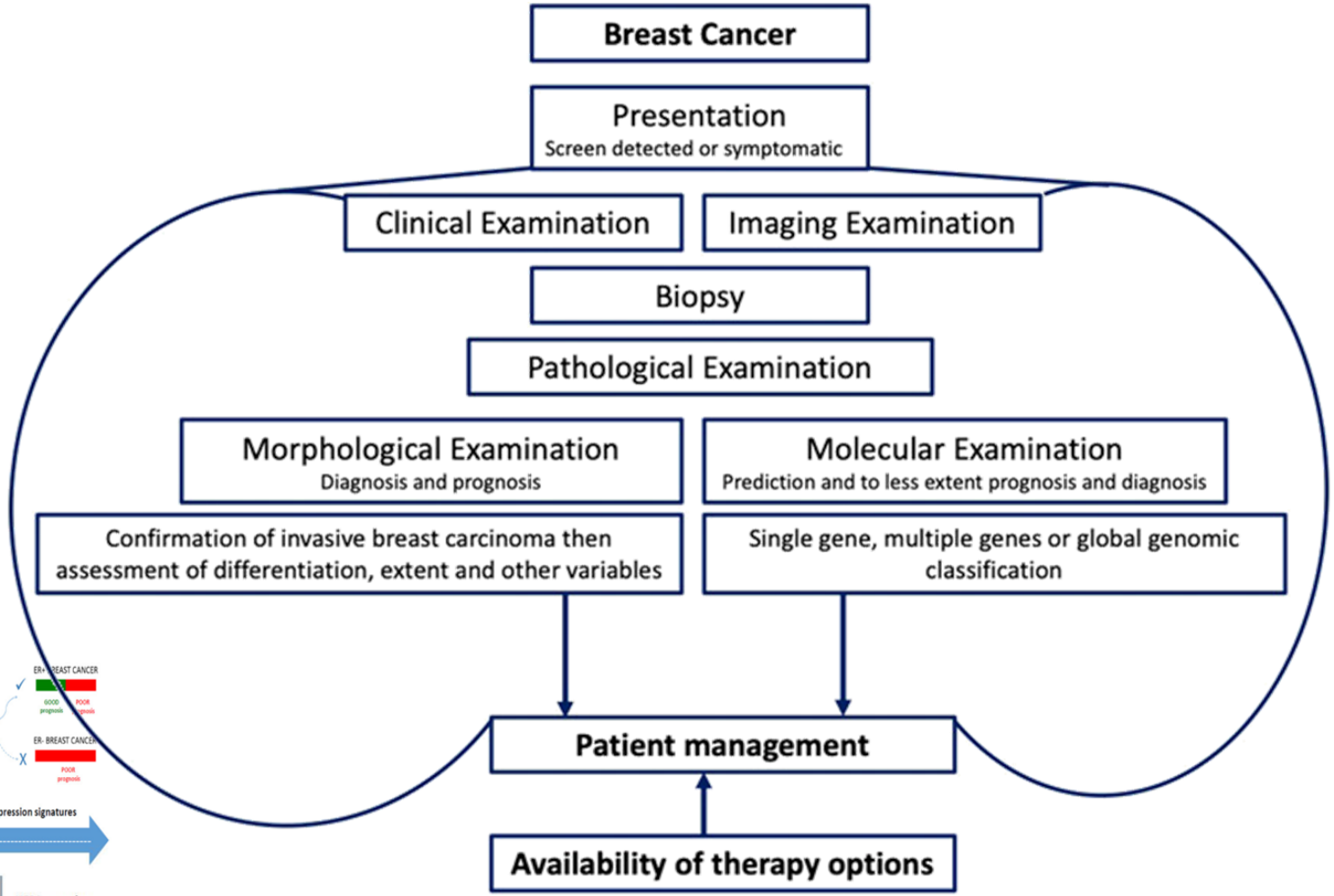
Hotel Leon d'Oro

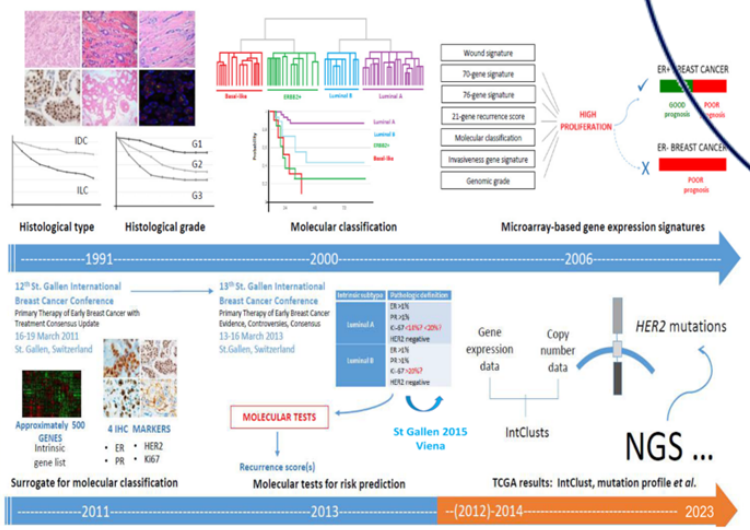
DISCLOSURES

Commercial Interest	Relationships
MSD, Novartis, AstraZeneca, Diaceutics, Adicet Bio, Sysmex, Roche, Menarini, Gilead, Veracyte Inc, Sakura.	Consulting/advisory role
MSD, Novartis, AstraZeneca, Daiichi Sankyo, GSK, Gilead, Roche, Leica Biosystems, Lilly, Pfizer.	Speaker bureau
Novartis, Reply, Gilead, AstraZeneca, GSK, Pfizer.	Research grants
Roche.	Travel grants

BC BIOMARKERS IN 2024

- The pathology report
- HRs (ER/PgR), Ki67
- HER2 spectrum
- PD-L1 (CPS/IC)
- PIK3CA (& pathway)
- ESR1
- gBRCA

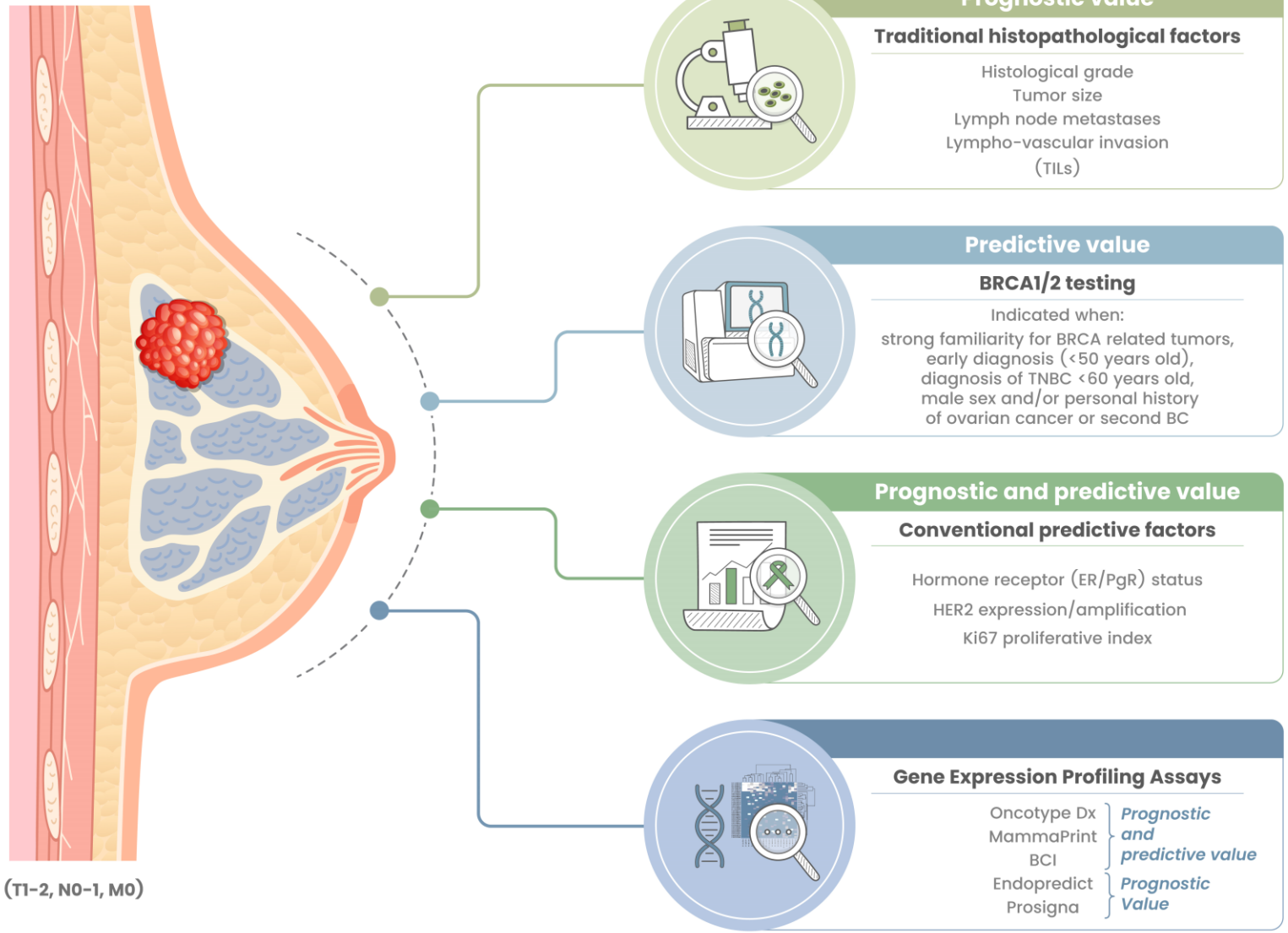





Histopathology

An update on the pathological classification of breast cancer

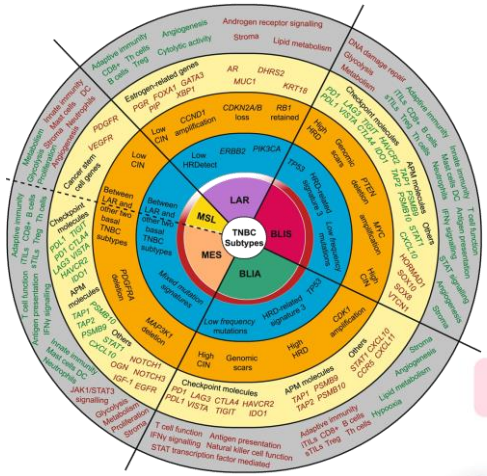
RISK STRATIFICATION (EARLY BREAST CANCER)



Type of tumour	Method
Most early breast cancers	BCS is the preferred local treatment option
Early, clinically node-negative breast cancer	• SLNB is the standard of care for axillary staging • If positive SLNB, further axillary surgery is not required for low axillary disease burden, axillary RT is an alternative
DCIS	BCS (with a 2 mm margin) followed by WBRT or total mastectomy are acceptable treatment options
Occult breast cancer	ALND and WBRT are the preferred locoregional management

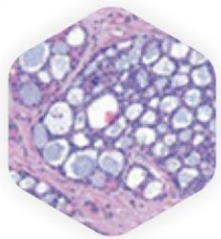
- Pathology remains the cornerstone → Ensuring an accurate diagnosis through pathology evaluation
- Lymph node examination (SLN + clinical) → staging and prognosis
- Identifying genetic factors that may contribute to breast cancer risk → BRCA
- Molecular tests only in alignment with established guidelines.

Pescia, Viale, and Fusco, Cancers 2023

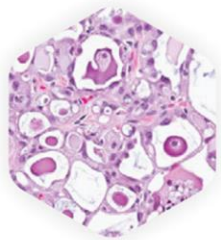


LOW-RISK TNBC

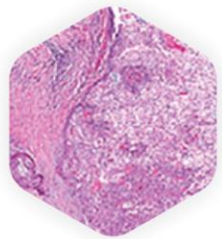
Salivary-gland like and rare subtypes



AdCC



Secretory



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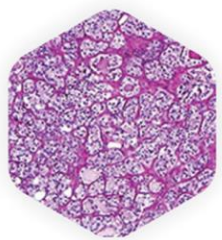

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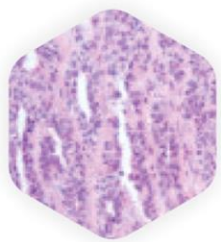
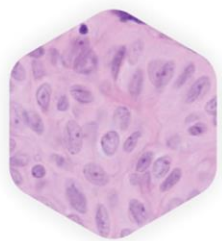
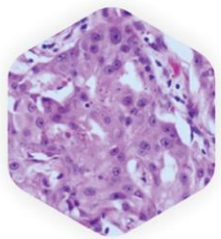


PmA

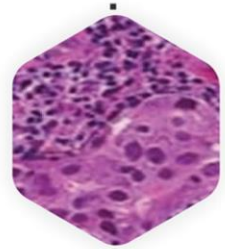


TCCRP

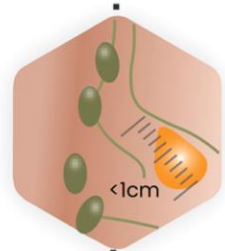
Apocrine



High TILs

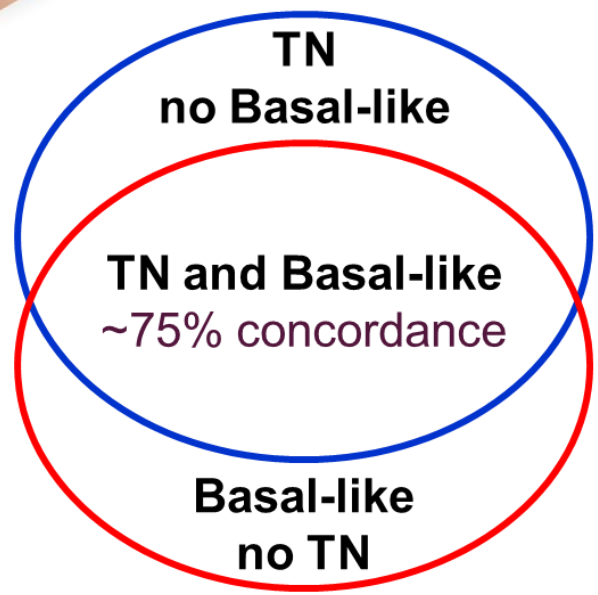


pT1a/bN0



Histological features

Clinical setting



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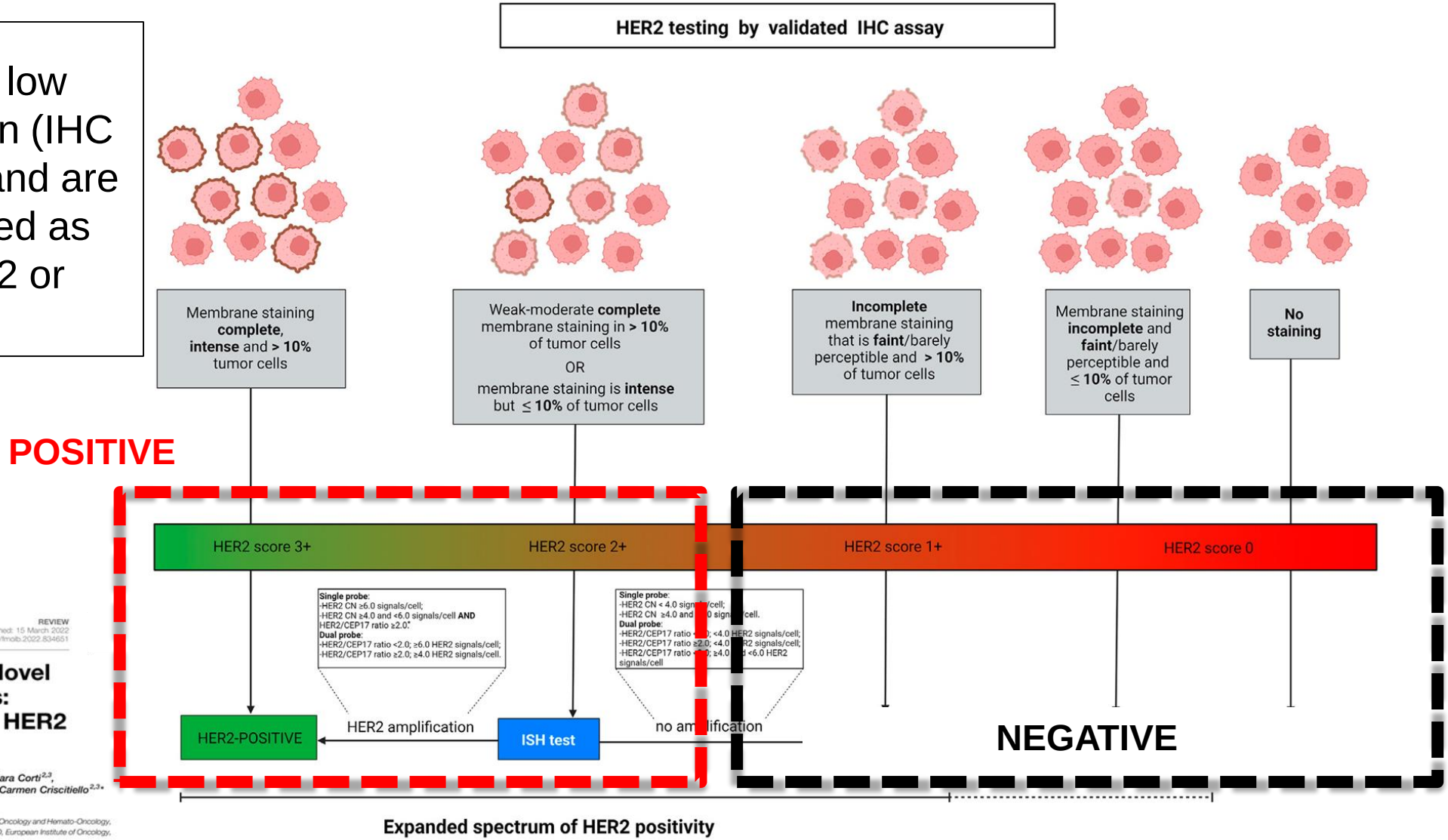
Low-risk triple-negative breast cancers: Clinico-pathological and molecular features

Nicola Fusco [a,b,*], Elham Sajjadi [a,b], Konstantinos Venetis [a,b], Mariia Ivanova [a], Silvia Andaloro [a], Elena Guerini-Rocco [a,b], Emilia Montagna [c], Pietro Caldarella [d], Paolo Veronesi [b,d], Marco Colleoni [c], Giuseppe Viale [a,b]

THE EXPANDED SPECTRUM OF HER2 POSITIVITY

~50% BCs have low HER2 expression (IHC 1+ or 2+/ISH-), and are currently classified as either HR+/HER2 or TNBC



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REVIEW
published: 15 March 2022
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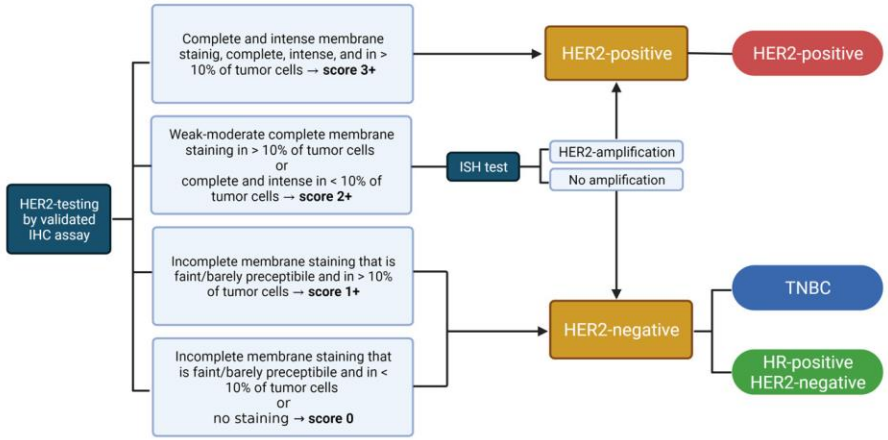
HER2 Low, Ultra-low, and Novel Complementary Biomarkers: Expanding the Spectrum of HER2 Positivity in Breast Cancer

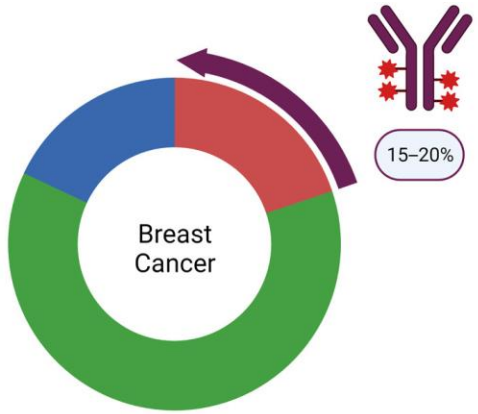
Konstantinos Venetis[1,2†], Edoardo Crimini[2,3†], Elham Sajjadi[1,2], Chiara Corti[2,3], Elena Guerini-Rocco[1,2], Giuseppe Viale[1,2], Giuseppe Curigliano[2,3], Carmen Criscitiello[2,3] and Nicola Fusco[1,2*]*

[1]Division of Pathology, IEO, European Institute of Oncology IRCCS, Milan, Italy, [2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy, [3]Division of Early Drug Development for Innovative Therapy, IEO, European Institute of Oncology, IRCCS, Milan, Italy

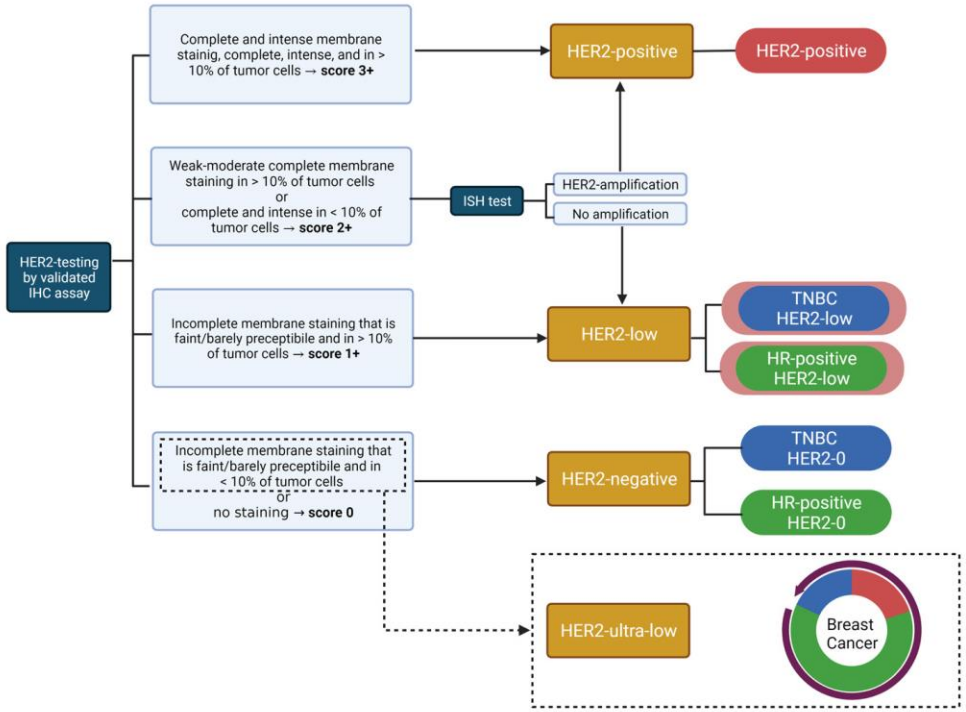
CLASSIFICATION OF BREAST CANCER AND ACCESS TO ANTI-HER2 DRUGS

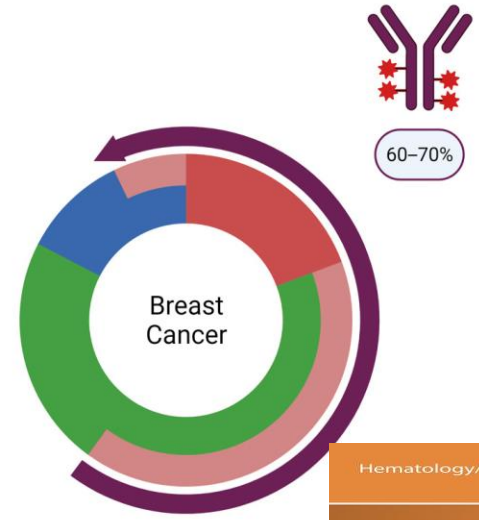
TODAY



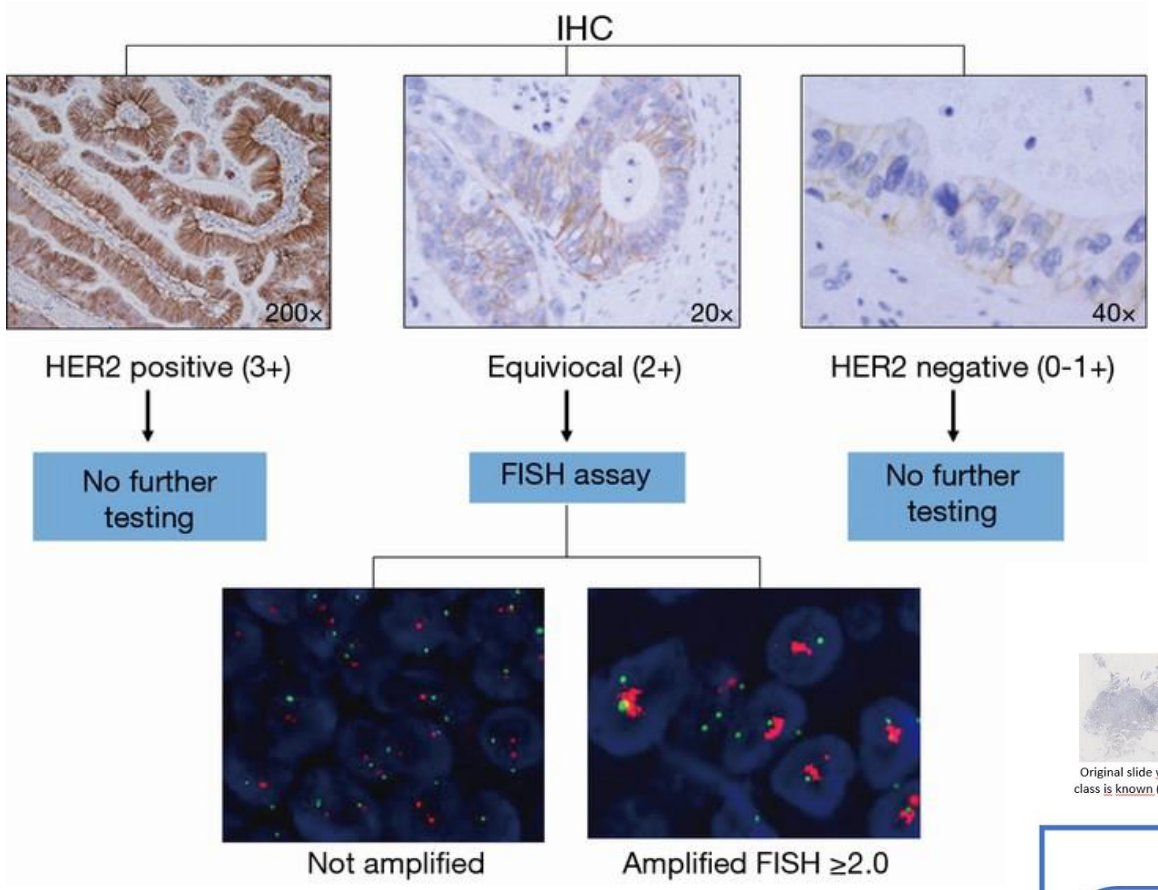


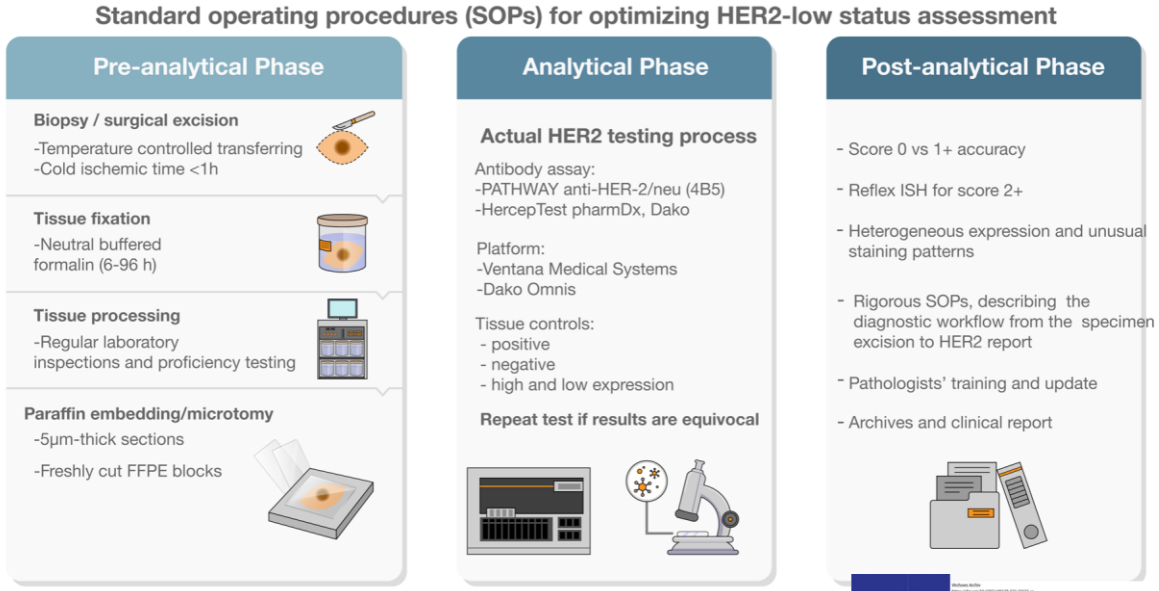
TOMORROW

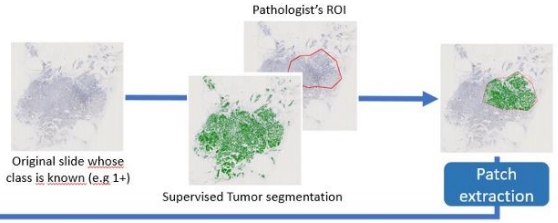




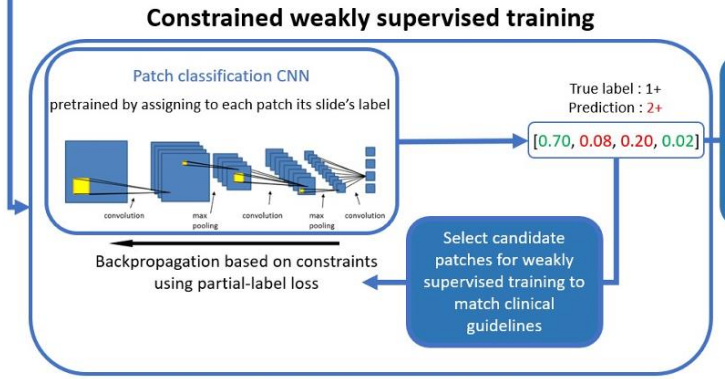
HOW TO TEST HER2?

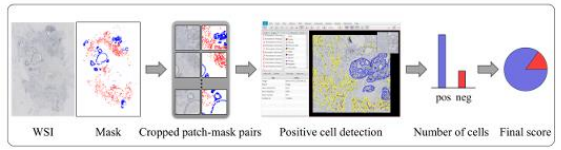






Slide label	Constraints on tumor surface fraction by HER2 score			
	0	1+	2+	3+
0	≥ 70%	< 10%	< 10%	< 10%
1+	-	≥ 10%	< 10%	< 10%
2+	-	-	≥ 10%	< 10%
3+	-	-	-	≥ 10%





Mod Pathol 35, 23–32 (2022).
Comput Med Imaging Graph . 2023

Sajadi et al. Cancer Drug Resist 2022;5:xx
DOI: 10.20517/cdr.2022.29

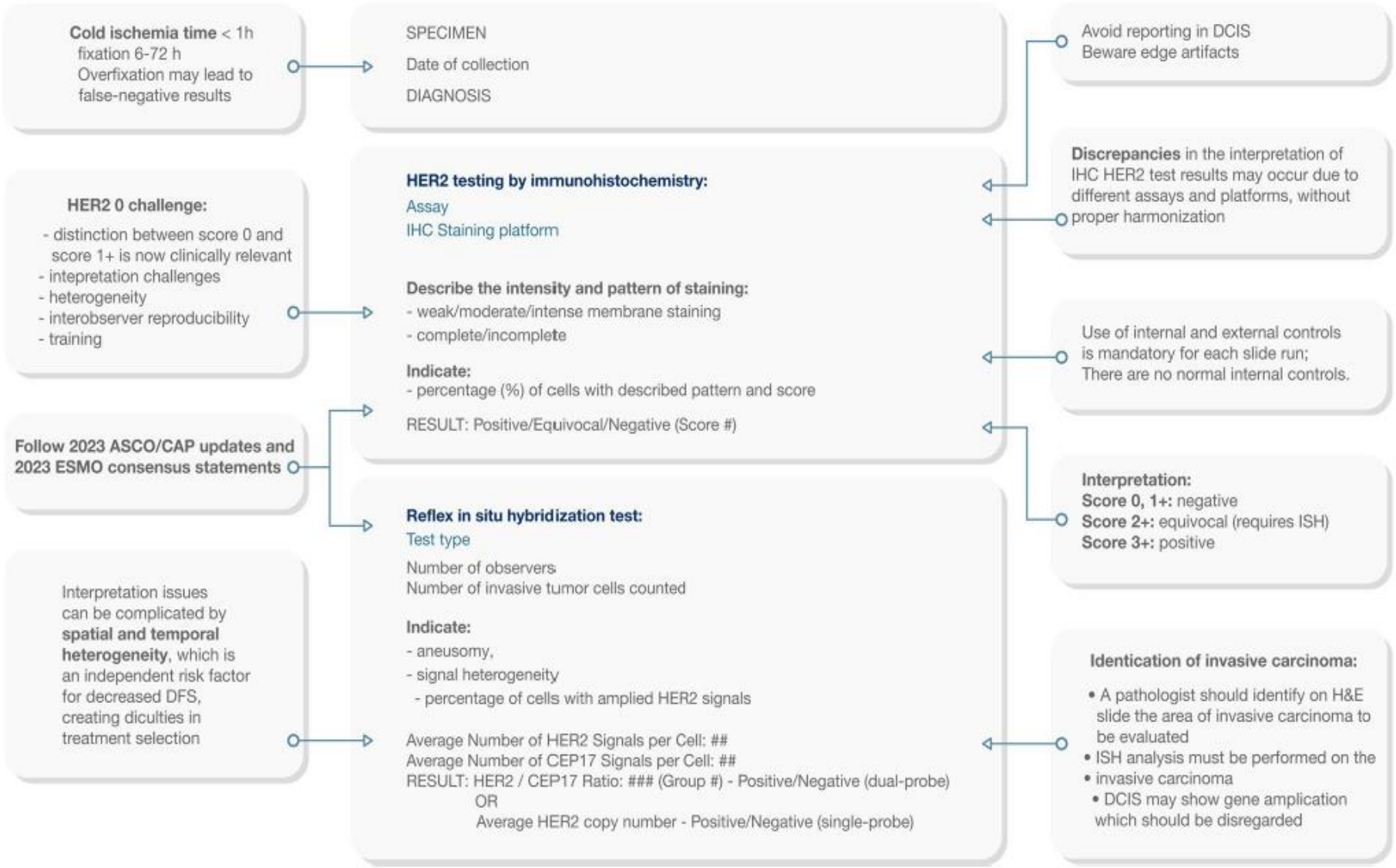
Cancer Drug Resistance

Improving HER2 testing reproducibility in HER2-low breast cancer

Elham Sajjadi[1,2], Konstantinos Venetis[1,2], Mariia Ivanova[1], Nicola Fusco[1,2]

[1]Division of Pathology, IEO, European Institute of Oncology IRCCS, Milan 20141, Italy.
[2]Department of Oncology and Hemato-Oncology, University of Milan, Milan 20122, Italy.

SYNOPTIC REPORT FOR HER2 TEST TO ADDRESS THE EVOLVING CLINICAL RATIONALE



Challenges to be addressed:

- Different antibodies and detection systems
- Different platforms
- Different scoring systems (ASCO/CAP vs Ventana)
- Spatial and temporal heterogeneity

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

Mariia Ivanova[1] · Francesca Maria Porta[1] · Marianna D'Ercole[1] · Carlo Pescia[1] · Elham Sajjadi[1,2] · Giulia Cursano[1] · Elisa De Camilli[1] · Oriana Pala[1] · Giovanni Mazzarol[1] · Konstantinos Venetis[1] · Elena Guerini-Rocco[1,2] · Giuseppe Curigliano[2,3] · Giuseppe Viale[1] · Nicola Fusco[1,2]

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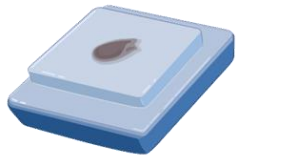
Virchows Archiv (2024) 484:3–14

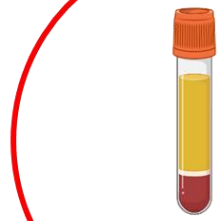
ESTABLISHED MOLECULAR BIOMARKERS IN BC

- As in early breast cancer, the quantity of ctDNA correlates with poor survival
- serial measurement of ctDNA has the potential to monitor and predict treatment response.
- mutation status of specific genes
  - **ESR1** (LB++, MT+)
  - **PIK3CA** (PT++, MT++, LB+)
  - HER2

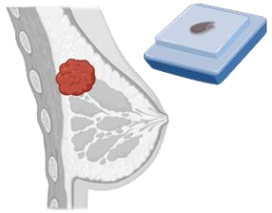
Which sample?



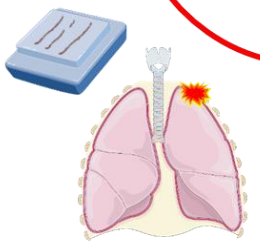
Histological specimen



Liquid biopsy

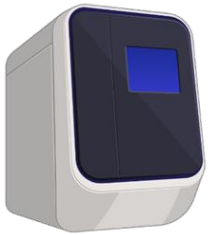


Primary tumor

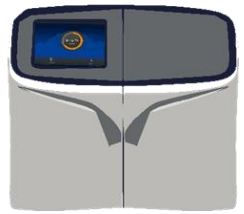


Metastatic sample

Which method?



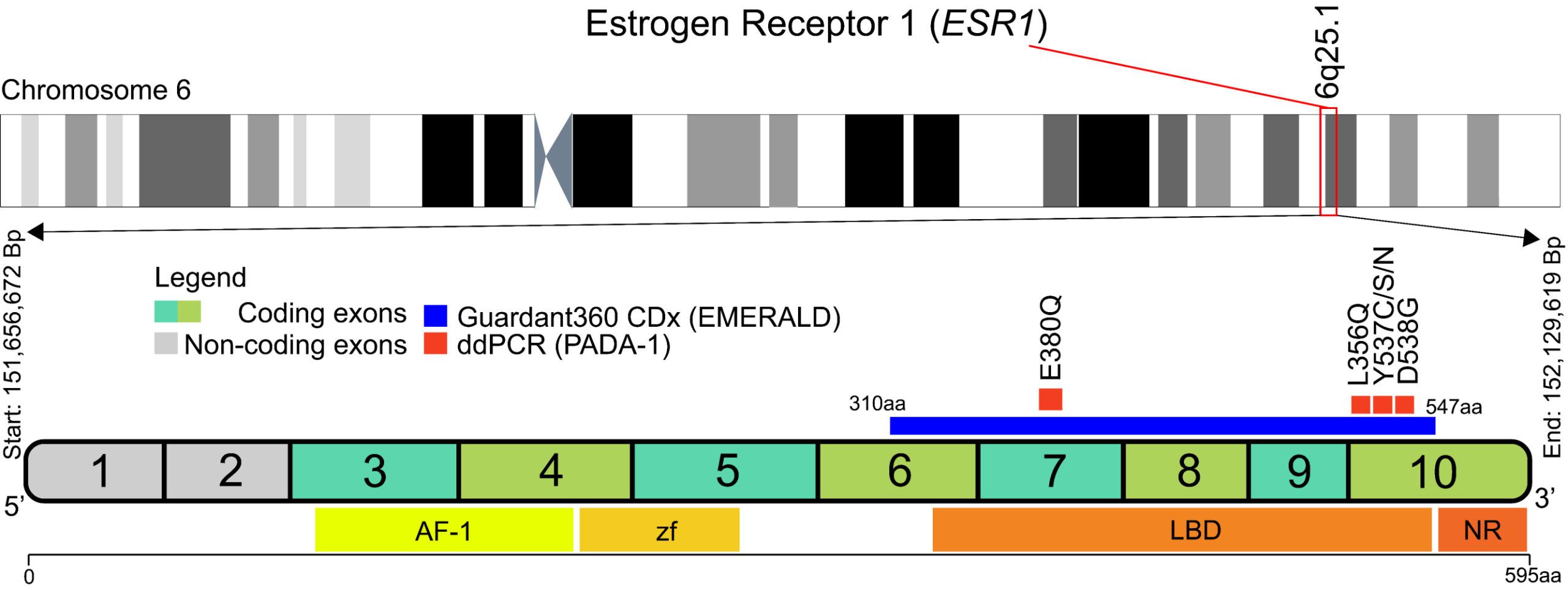
Digtal Droplet PCR



Next-Generation Sequencing

ESR1 TESTING ON LIQUID BIOPSY

- ESR1 mutations occurrence in LBD lead to ET resistance (mainly to AI)
- Rationale: to select patients with HR+/HER2- MBC for Elacestrant treatment



Venetis et al. Cancer Treat Rev 2023

HOW TO TEST ESR1?

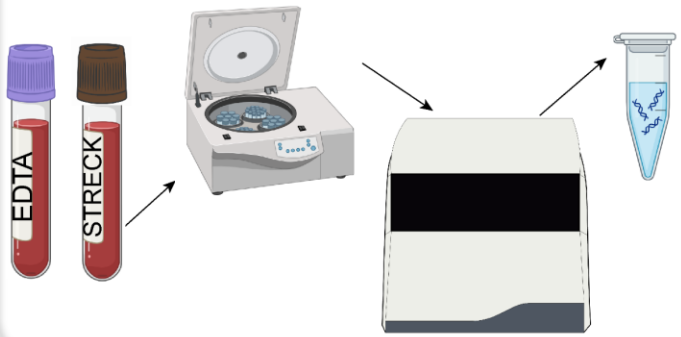
Pre-analytical Phase

Timing of blood sampling — disease progression

Collection tubes
- EDTA (need to be processed within 1 hour upon blood collection)
- Preservative tubes (up to 7 days at 6°C to 37°C)

Centrifugation → Two-step 2000 x g at 4° centrifugation 10' each

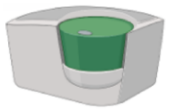
cfDNA extraction → Automated extraction methods are preferred over manual ones



Analytical Phase

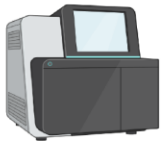
PCR-based approaches

- **LOD**: ddPCR up to 0.0001%; RT-PCR between 1% and 5%
- **TAT**: 3-5 days
- **Reportable range**: mainly hotspot codons 380, 536, 537, 538



NGS-based approaches

- **LOD**: between 0.1% to 1.1%
- **TAT**: around 7 days
- **Reportable range**: multiple *ESR1* exons to full gene coverage



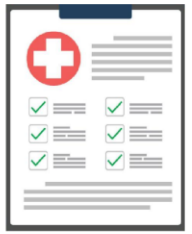
In case of *ESR1* wt consider retesting of patients at subsequent progression(s)

Post-analytical Phase

- Result → WT
- Result → Mutated → specific mutation

clinical annotation + ESCAT Score
- oncogenic
- likely oncogenic
- VUS
- likely neutral

- Contextualization of mutations detected below the reportable cut-off values
- Rigorous SOPs, describing the diagnostic workflow from the blood collection to *ESR1* report
- Collaboration between pathologists and molecular biologists
- Clinical report



SYNOPTIC REPORT FOR ESR1 TEST IN 2024

Collection tubes
- **EDTA** (processed within 1 hour from collection)
- **Preservative tubes** (up to 7 days)

Centrifugation
Two-step 2000 x g at 4° centrifugation 10' each

Specimen
Date of collection
Diagnosis
Name
Surname
Gender
Date of birth
Age

Molecular biology analysis (NGS/ddPCR)
Provide the following technical notes:
- Type of NGS panel/ddPCR assay
- Reportable range: list of analyzed genes/hotspot regions
- Type of alterations
  - Hotspot mutations
  - Copy number alterations
  - Gene fusion
- Type of sequencing (Hybrid-capture, Amplicon-based)
- Analysis software

Nucleic acids extraction
- Platform and kit for cfDNA extraction
- Cut-off values for cfDNA quantity
- Circulating tumor fraction

***ESR1* testing by ddPCR/NGS**
Assay
Sequencing platform
Describe the quantity and quality of extracted nucleic acids
- adequate/suboptimal/low (ng/µl)
- degree of fragmentation

Indicate
- circulating tumor cell fraction

Aknowledge limitations of the method
- Sensibility: not able to identify alterations below a certain limit of detection
- Types of alterations not able to be detected (e.g. large deletions and duplications)

ASCO Rapid Recommendations updates for *ESR1* testing

In case of *ESR1* wt consider retesting of patients at subsequent progression(s)

Interpretation notes
- International nomenclature (HGVS)
- VAF (Cut-off values have to be set for mutation reporting)

Results
ESR1 mutated/wt
Mutation detected (exon/protein change/codon change/NM/VAF/Level)
Concomitant mutations (e.g., *PIK3CA)*

ESCAT levels

HOW TO TEST PIK3CA?

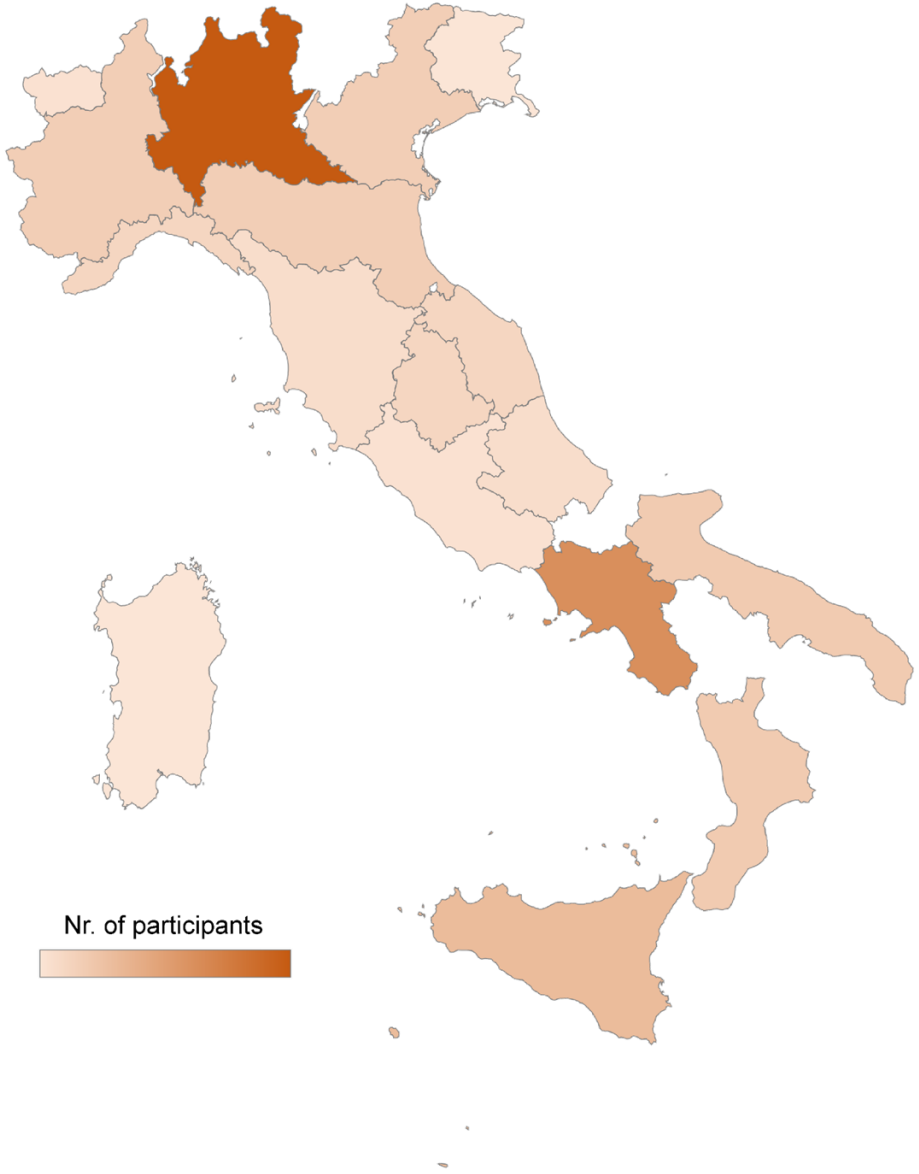
RT-PCR

PROS	CONS
• Cost-effective • Short turnaround time • Widely available • High sensitivity • Wide choice of panels	• High amount of material required • Affected by low tumor cell content • Variable reference range • No allele frequency • Affected by the pre-analytical phase

Next-Generation Sequencing

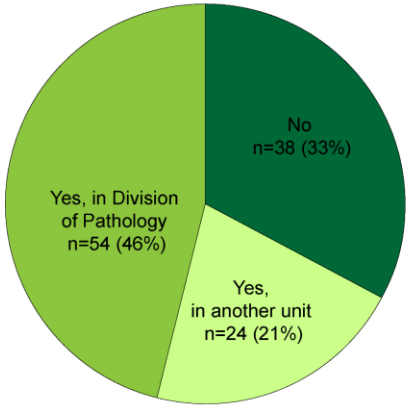
PROS	CONS
• Higher sequencing depth for increased sensitivity (down to 1%) • Multi-target panels • Low input of nucleic acid needed • Wide choice of panels	• Expensive • Long turnaround time • Not widely available • Affected by the pre-analytical phase • Dedicated personnel required

LANDSCAPE OF CURRENT PIK3CA MOLECULAR TESTING IN BC– NATIONWIDE SURVEY (138 CENTERS)

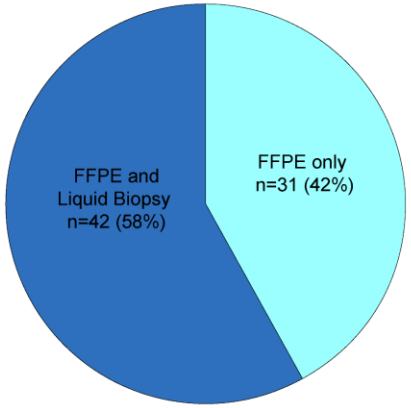


North-west	**52**
Valle d'Aosta	2
Piemonte	7
Lombardia	38
Liguria	5
North-east	**15**
Veneto	7
Friuli Venezia Giulia	1
Emilia Romagna	7
Center	**18**
Toscana	3
Umbria	5
Marche	5
Lazio	2
Abruzzo	3
South and islands	**53**
Campania	24
Puglia	8
Calabria	8
Sardegna	1
Sicilia	12

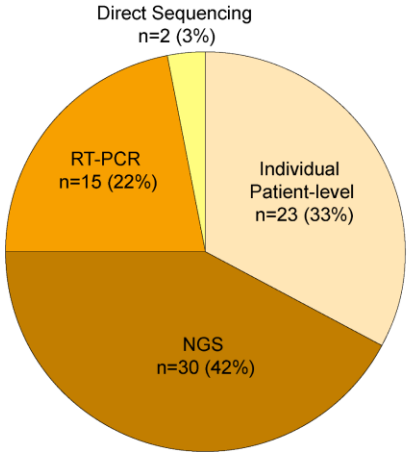
Q1: Do you have the possibility to carry out the test in your center?
n=116 answers



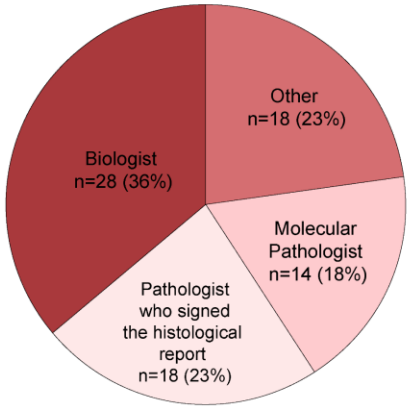
Q2: On which biomaterial can you conduct the analysis?
n=73 answers



Q3: Which technology is adopted for this test?
n=70 answers



Q4: Which professionals sign the clinical report of this molecular test for breast cancer in your center ?
n=78 answers



Pepe et al. Pharmacogenomics 2024

Landscape of current PIK3CA molecular testing in BC– Real World Data

Future Medicine Ltd
Pharmacogenomics
Preprint, February 2024
https://doi-org.pros2.lib.unimi.it/10.2217/pgs-2023-0238

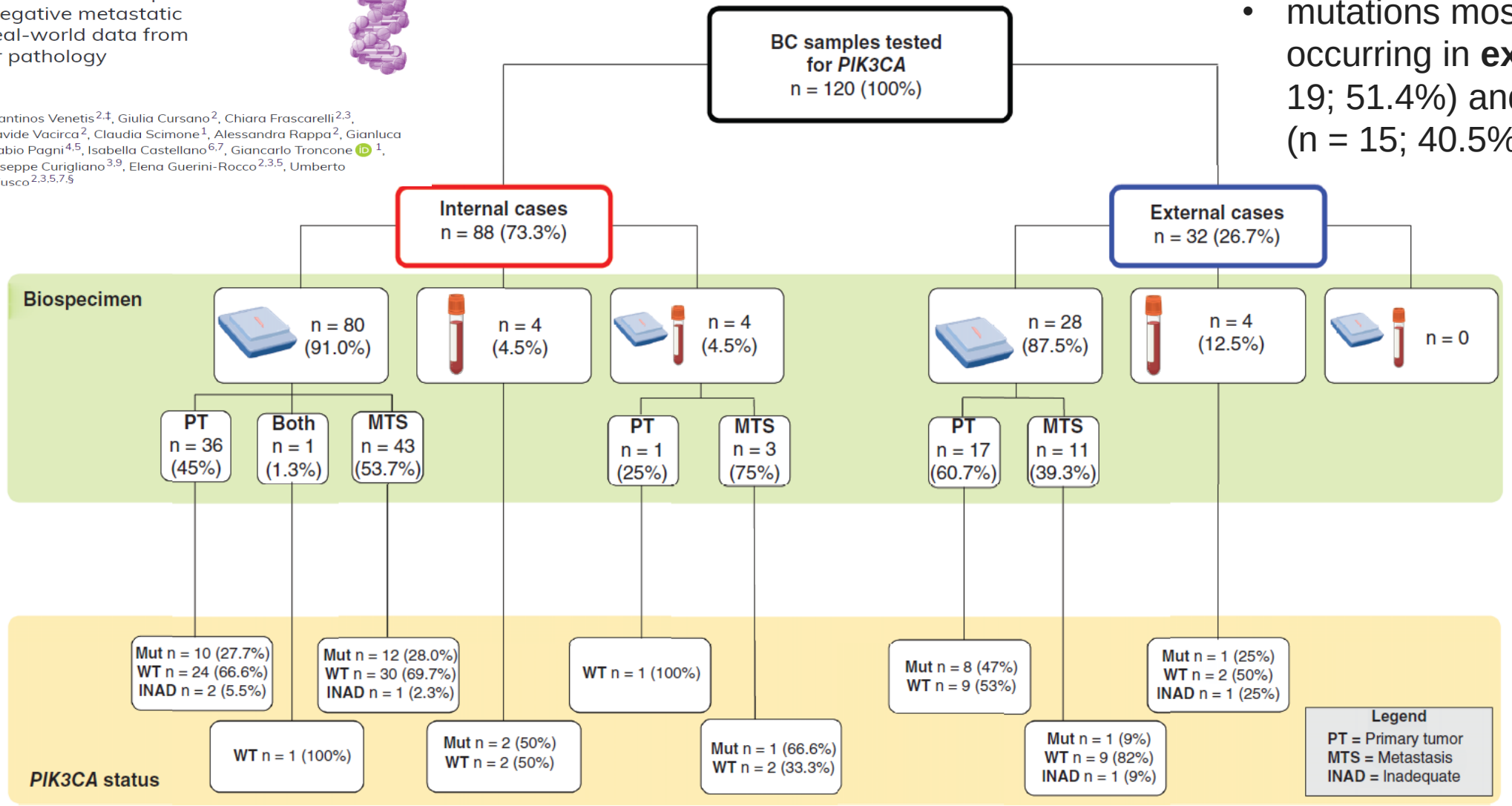
Research Article

Pharmacogenomics

PIK3CA testing in hormone receptor-positive/HER2-negative metastatic breast cancer: real-world data from Italian molecular pathology laboratories

Francesco Pepe[1,‡], Konstantinos Venetis[2,‡], Giulia Cursano[2], Chiara Frascarelli[2,3], Pasquale Pisapia[1], Davide Vacirca[2], Claudia Scimone[1], Alessandra Rappa[2], Gianluca Russo[1], Eltjona Mane[2], Fabio Pagni[4,5], Isabella Castellano[6,7], Giancarlo Troncone[1], Carmine De Angelis[8], Giuseppe Curigliano[3,9], Elena Guerini-Rocco[2,3,5], Umberto Malapelle[1,5,*,§] & Nicola Fusco[2,3,5,7,§]

- 28% MBCs were *PIK3CA*-mut
- mutations mostly occurring in **exon 9** (n = 19; 51.4%) and **exon 20** (n = 15; 40.5%).



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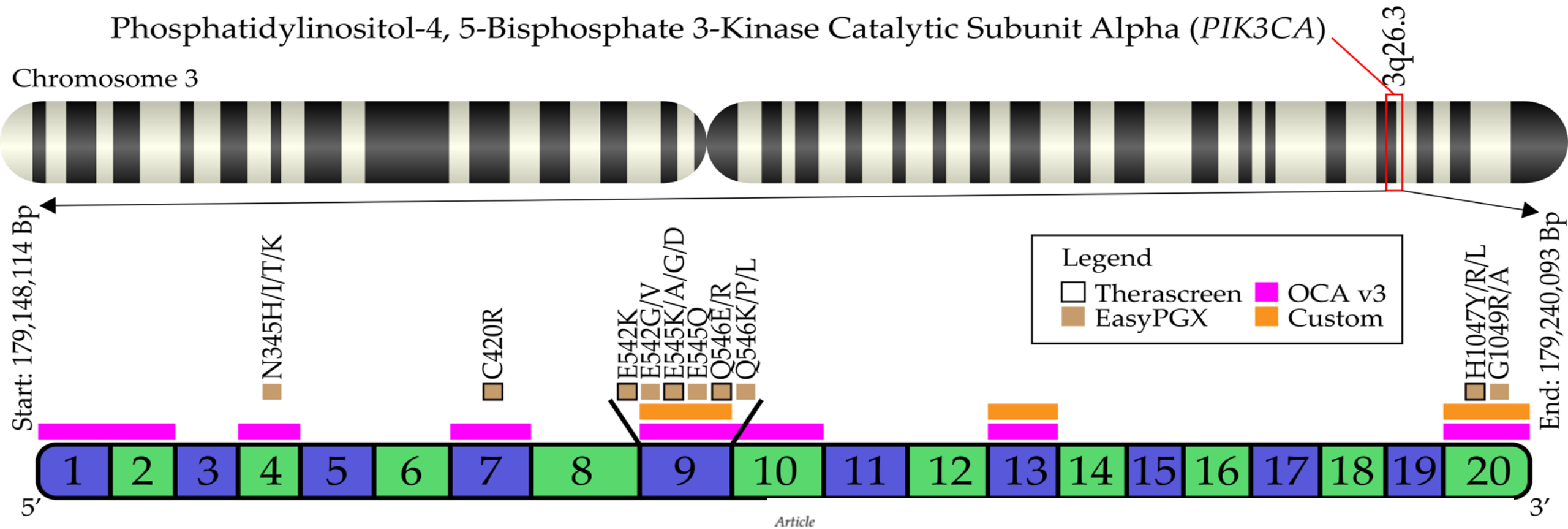
FEDERICO II

PIK3CA MUTATIONS IN BREAST CANCERS: TESTING STRATEGIES



Article

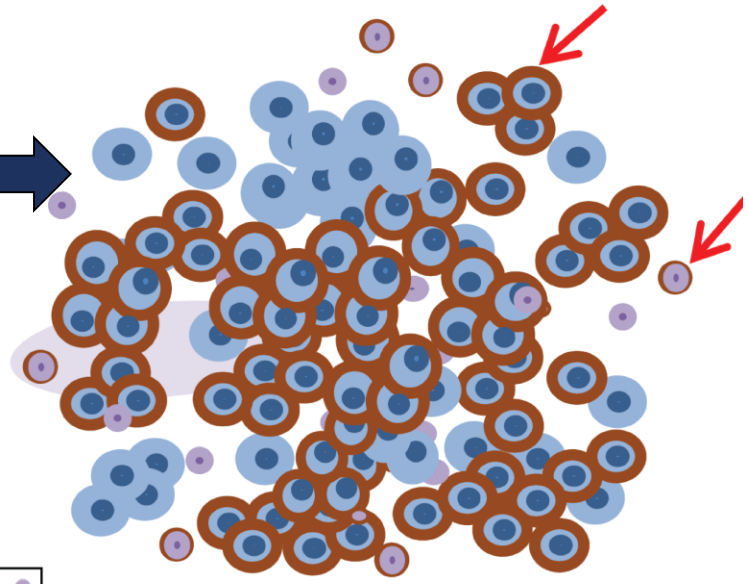
Analytical Performance of Next-Generation Sequencing and RT-PCR on Formalin-Fixed Paraffin-Embedded Tumor Tissues for *PIK3CA* Testing in HR+/HER2− Breast Cancer

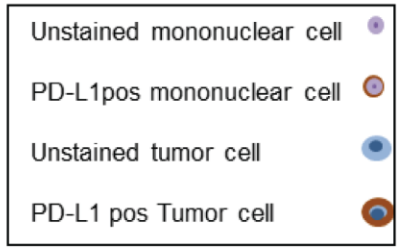
Konstantinos Venetis [1,2,†], Francesco Pepe [3,†], Elisabetta Munzone [4], Elham Sajjadi [1,2], Gianluca Russo [3], Pasquale Pisapia [3], Mariia Ivanova [1], Giuseppina Bonizzi [1], Davide Vacirca [1], Alessandra Rappa [1], Alberto Ranghiero [1], Sergio Vincenzo Taormina [1], Giuseppe Viale [1,2], Giancarlo Troncone [3], Massimo Barberis [1], Elena Guerini-Rocco [1,2], Umberto Malapelle [3,*,‡] and Nicola Fusco [1,2,*,‡]

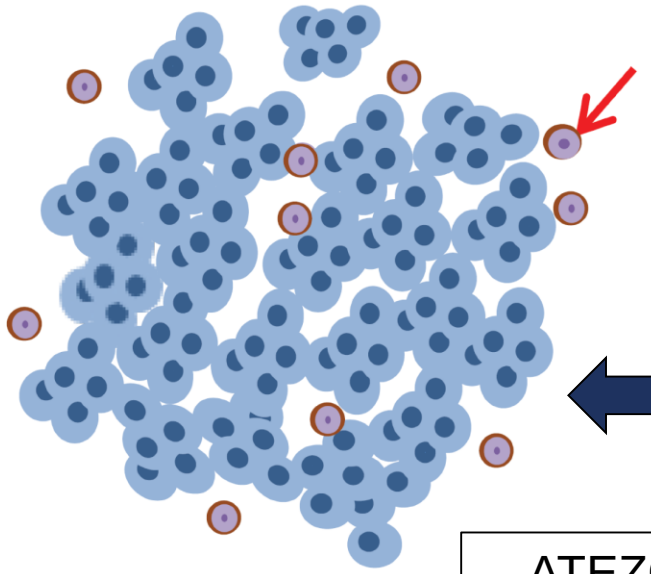
Cells. 2022 Nov 9;11(22):3545. doi: 10.3390/cells11223545.

PD-L1 TEST IN mTNBC

PEMBROLIZUMAB







ATEZOLIZUMAB

CPS

$$CPS = \frac{\text{PD- L1 staining} \left[\begin{array}{l}\text{Tumor cells}\\ \text{Lymphocytes}\\ \text{Macrophages}\end{array}\right]}{\text{viable tumor cells}} 100$$

IC

$$IC = \frac{\text{PD- L1 staining} \left[\begin{array}{l}\text{Plasma cells}\\ \text{Lymphocytes}\\ \text{Macrophages}\end{array}\right]}{\text{tumor area}} 100$$

Validated assays for CPS:

- Ventana SP263
- Dako 22-C3

TNBCs are scored and divided into:

CPS < 10 IC < 1

CPS ≥ 10 IC ≥ 1

Validated assays for IC:

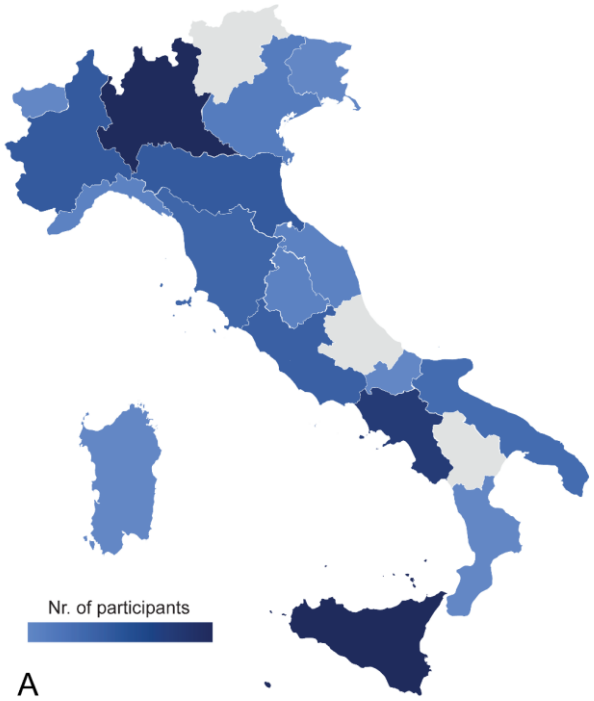
- Ventana SP142

ecancermedicalscience

Biomarkers for precision immunotherapy in the metastatic setting: hope or reality?

Elham Sajjadi[1,2], Konstantinos Venetis[1,2], Cristian Scatena[3] and Nicola Fusco[1,2]

LANDSCAPE OF CURRENT PD-L1 MOLECULAR TESTING IN TNBC– NATIONWIDE SURVEY (103 CENTERS)



North-west	**31**
Valle d'Aosta	1
Piemonte	9
Lombardia	19
Liguria	2
North-east	**13**
Veneto	3
Friuli Venezia Giulia	1
Emilia Romagna	9
Center	**19**
Toscana	7
Umbria	2
Marche	2
Lazio	8
South and islands	**43**
Molise	1
Campania	15
Puglia	6
Calabria	1
Sardegna	1
Sicilia	19

Critical Reviews in Oncology / Hematology 190 (2023) 104103

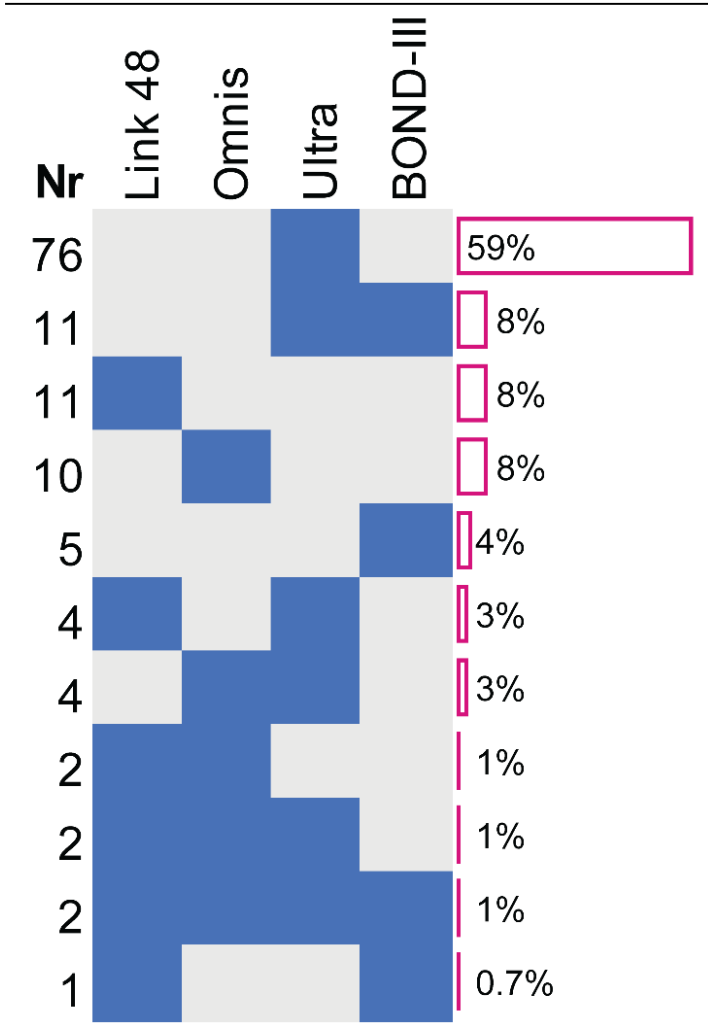
Contents lists available at ScienceDirect

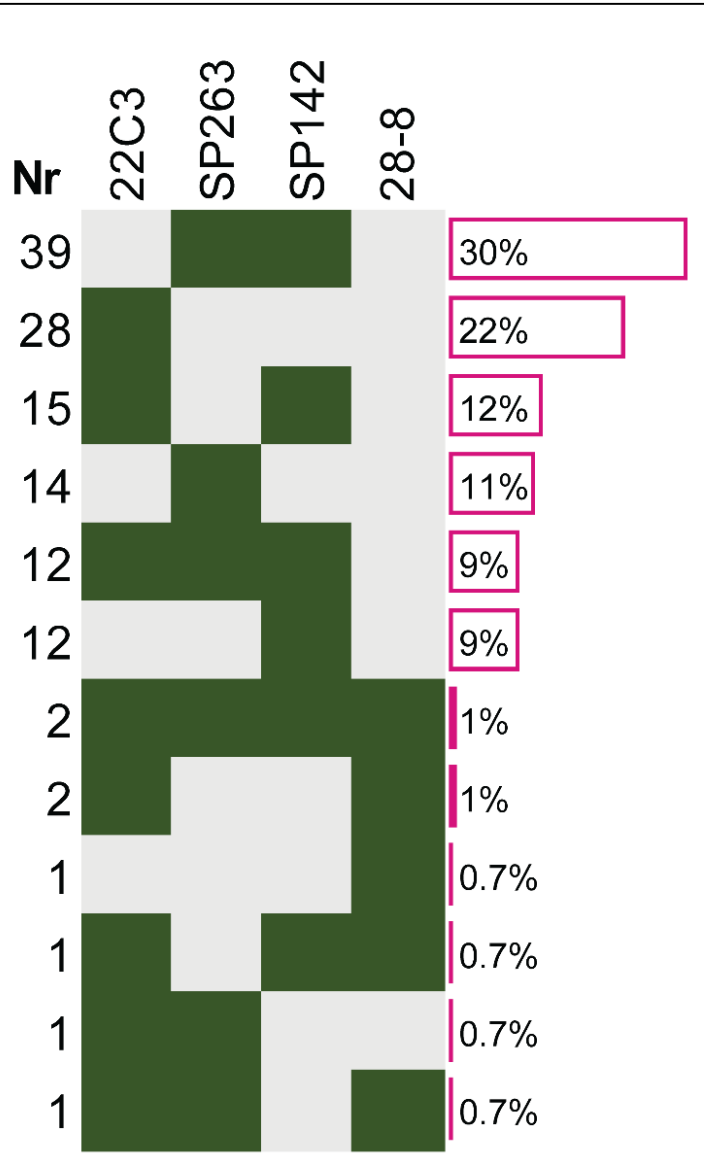
Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

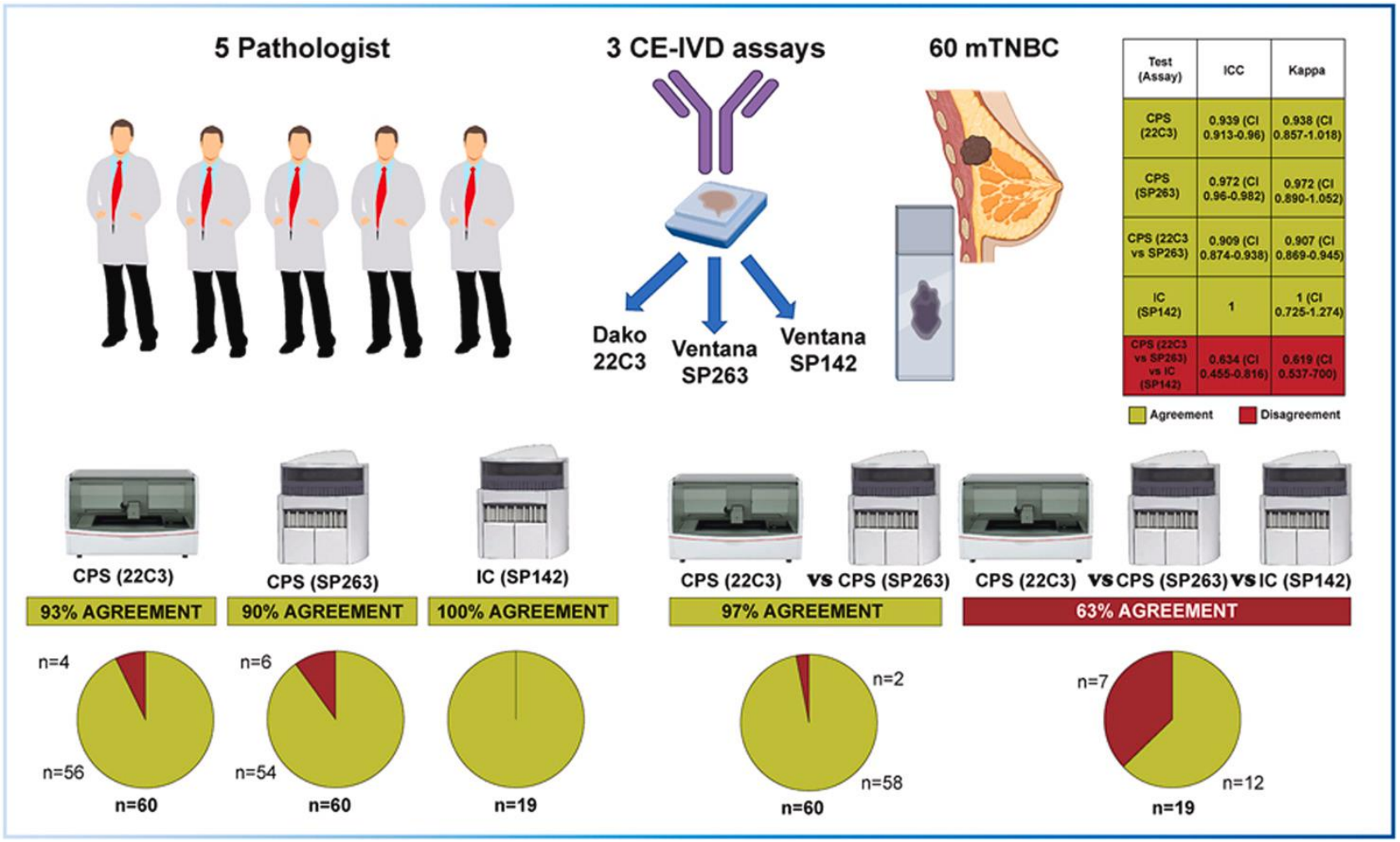
Advancing the PD-L1 CPS test in metastatic TNBC: Insights from pathologists and findings from a nationwide survey

Nicola Fusco [a,b,*], Mariia Ivanova [a], Chiara Frascarelli [a,b], Carmen Criscitiello [a,c], Bruna Cerbelli [d], Maria Gemma Pignataro [d], Angelina Pernazza [d], Elham Sajjadi [a,b], Konstantinos Venetis [a], Giulia Cursano [a], Fabio Pagni [e,f], Camillo Di Bella [f], Marina Accardo [g], Michelina Amato [h], Paolo Amico [i], Caterina Bartoli [j], Giuseppe Bogina [k], Laura Bortesi [k], Renzo Boldorini [l], Sara Bruno [m], Daniela Cabibi [n], Pietro Caruana [o], Emanuele Dainese [p], Elisa De Camilli [a], Vladimiro Dell'Anna [q], Loren Duda [r], Carmela Emmanuele [s], Giuseppe Nicolò Fanelli [t], Bethania Fernandes [u], Gerardo Ferrara [v], Letizia Gnetti [s], Alessandra Gurrera [w], Giorgia Leone [x], Raffaella Lucci [y], Cristina Mancini [s], Grazia Marangi [z], Mauro G. Mastropasqua [aa], Lorenzo Nibid [ab,ac], Sandra Orrù [ad], Maria Pastena [ae], Monica Peresi [af], Letizia Perracchio [ag], Angela Santoro [ah], Vania Vezzosi [ai], Claudia Zambelli [aj], Valeria Zuccalà [ak], Antonio Rizzo [x], Leopoldo Costarelli [h], Francesca Pietribiasi [al], Alfredo Santinelli [am], Cristian Scatena [t], Giuseppe Curigliano [b,c], Elena Guerini-Rocco [a,b], Maurizio Martini [am], Paolo Graziano [ao], Isabella Castellano [ap], Giulia d'Amati [d]





PD-L1 TEST ANALYTICAL VALIDATION IN mTNBC



- In mTNBC, CPS can be reliably assessed either by 22C3 (which was used in the KEYNOTE studies) or SP263, providing the use of the dedicated platform (i.e. Dako and Ventana).
- CPS and IC are not interchangeable tests in mTNBC
- PD-L1 test in mTNBC is reproducible when assessed by specifically trained pathologists using CE-IVD assays, i.e. 22C3 and SP263 for CPS and SP142 for IC score.

Human Pathology 144 (2024) 22–27

Contents lists available at ScienceDirect

Human Pathology

journal homepage: www.elsevier.com/locate/humpath

PD-L1 testing in metastatic triple-negative breast cancer: Interobserver and interplatform reproducibility of CE-IVD assays for CPS and IC scores

Mariia Ivanova [a,1], Chiara Frascarelli [a,b,1], Bruna Cerbelli [c,1], Maria Gemma Pignataro [c], Angelina Pernazza [c], Konstantinos Venetis [a], Elham Sajjadi [a,b], Carmen Criscitiello [b,d], Giuseppe Curigliano [b,d], Elena Guerini-Rocco [a,b], Paolo Graziano [e], Maurizio Martini [f], Giulia d'Amati [c,2], Nicola Fusco [a,b,*,2]

ER^{LOW} BC: HOW TO TEST FOR ER?

Invasive carcinomas with low level (1-10%) of ER expression

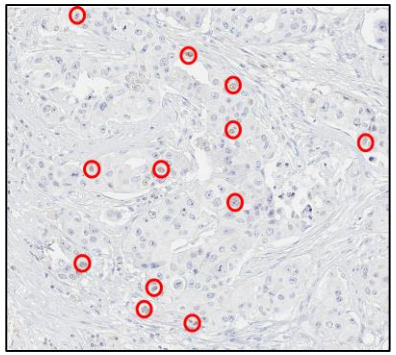
2-3% of ER^+ invasive breast cancers

Clinically challenging

>> Heterogeneous behavior and biology

>> Gene expression and clinical profiles more similar to ER- cancers

>> Eligible for HT but limited data on the benefit



Diagnostically challenging

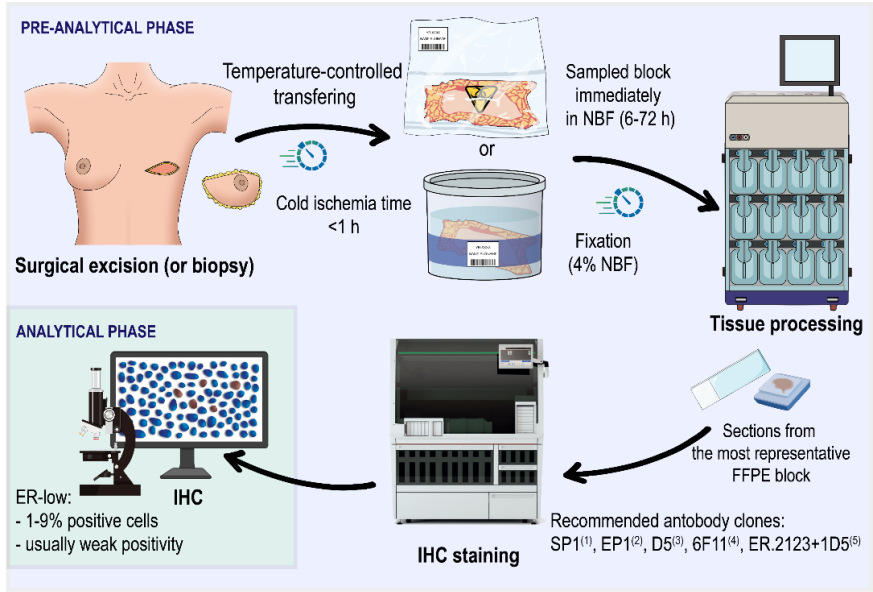
>> Usually weak/very weak nuclear staining

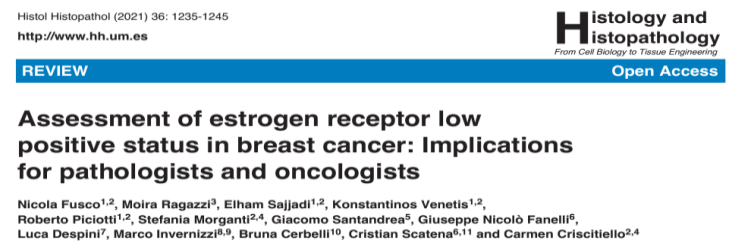
>> Pre-analytical issues

>> **Inter-observer reproducibility**

>> An additional comment should be provided in the pathology report

>> **Biology**



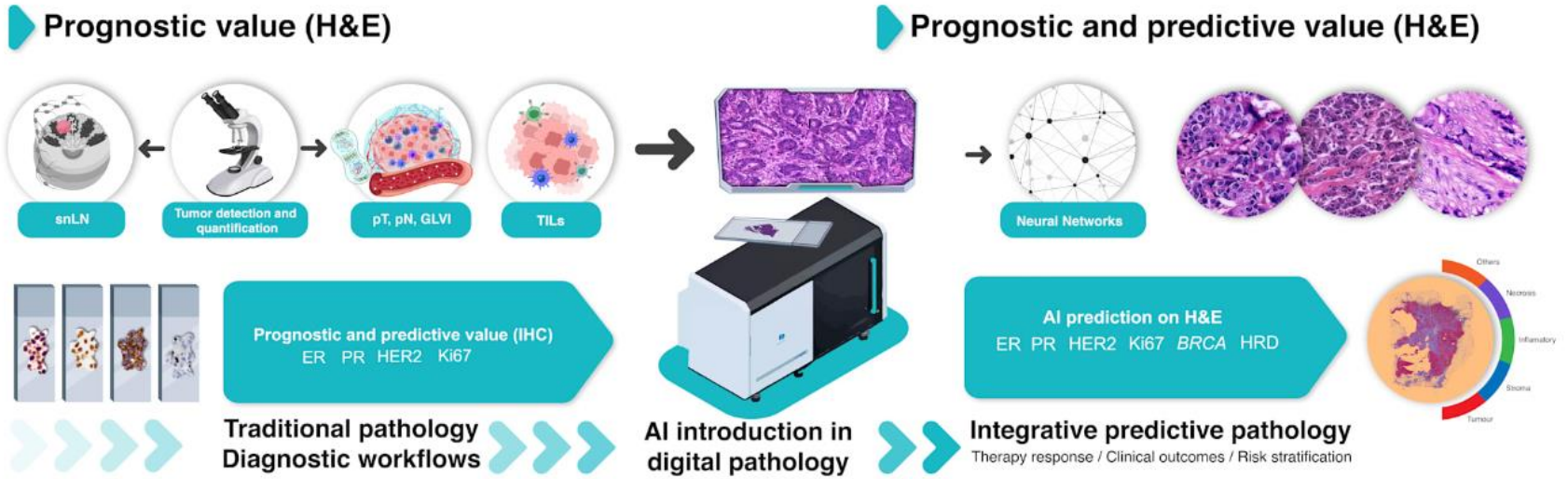

Histol Histopathol (2021) 36: 1235-1245
http://www.hh.um.es
Histology and Histopathology
From Cell Biology to Tissue Engineering
REVIEW
Open Access

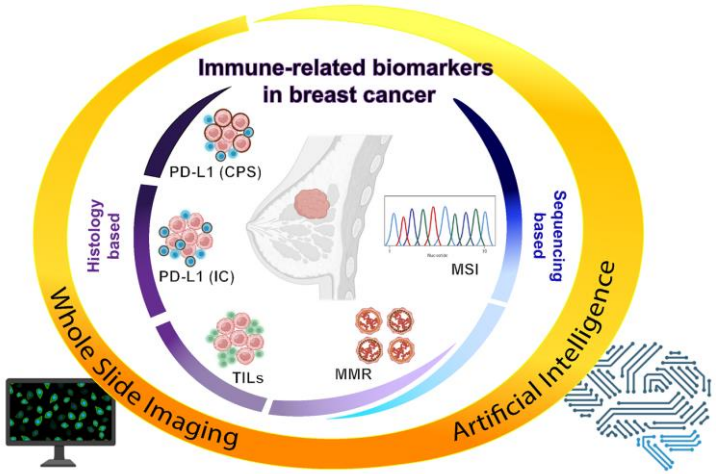
Assessment of estrogen receptor low positive status in breast cancer: Implications for pathologists and oncologists

Nicola Fusco[1,2], Moira Ragazzi[3], Elham Sajjadi[1,2], Konstantinos Venetis[1,2], Roberto Piciotti[1,2], Stefania Morganti[2,4], Giacomo Santandrea[5], Giuseppe Nicolò Fanelli[6], Luca Despini[7], Marco Invernizzi[8,9], Bruna Cerbelli[10], Cristian Scatena[8,11] and Carmen Criscitiello[2,4]

Allison et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline Update. JCO, Jan 2020

WHAT ROLE FOR AI-ASSISTED DIAGNOSIS AND BIOMARKERS TESTING IN BC?



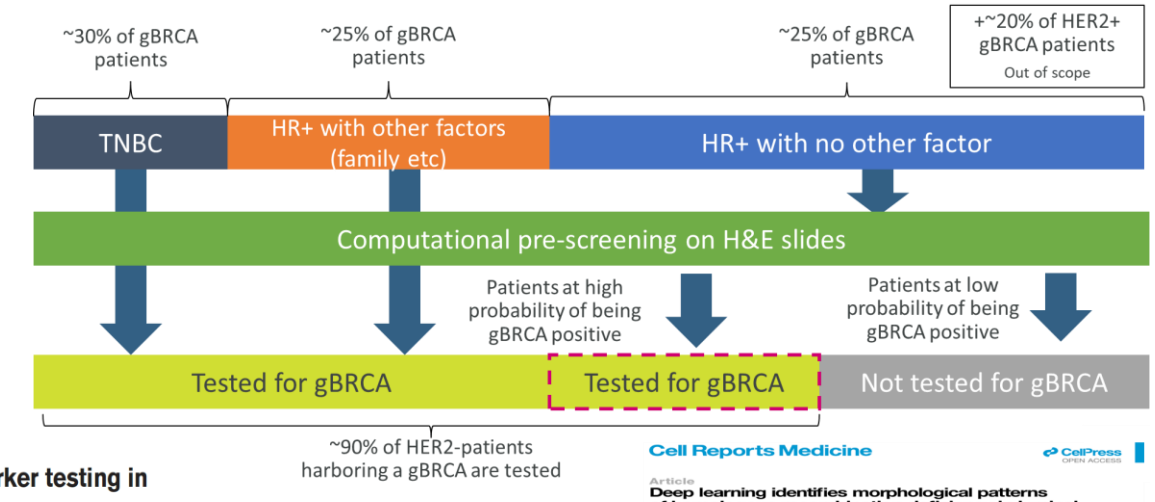


Journal of Personalized Medicine J. Pers. Med. 2023, 13, 1176. https://doi.org/10.3390/jpm13071176

Review

Immune Biomarkers in Triple-Negative Breast Cancer: Improving the Predictivity of Current Testing Methods

Francesca Maria Porta [1], Elham Sajjadi [1,2], Konstantinos Venetis [1], Chiara Frascarelli [1,2], Giulia Cursano [1], Elena Guerini-Rocco [1,2], Nicola Fusco [1,2,*] and Mariia Ivanova [1]



EUROPEAN JOURNAL OF CANCER PREVENTION
The Official Journal of the European Cancer Prevention Organisation (ECP)

Computational pathology to improve biomarker testing in breast cancer: how close are we?

Elham Sajjadi[a,b,*], Chiara Frascarelli[a,b,*], Konstantinos Venetis[b], Giuseppina Bonizzi[b], Mariia Ivanova[b], Gianluca Vago[a], Elena Guerini-Rocco[a,b,#] and Nicola Fusco[a,b,#]

Cell Reports Medicine
CellPress OPEN ACCESS

Article

Deep learning identifies morphological patterns of homologous recombination deficiency in luminal breast cancers from whole slide images

Tristan Lazard, Guillaume Bataillon, Peter Naylor, Tatiana Popova, François-Clément Bidard, Dominique Stoppa-Lyonnet, Marc-Henri Stern, Etienne Decencière, Thomas Walter, and Anne Vincent-Salomon

INTEGRATIVE ONCOLOGIC PATHOLOGY FOR THE CLINICAL MANAGEMENT OF TNBC

Balancing between:

- Classic morphology
- Molecular classification(s)
- Computer-assisted diagnostics

For clinical decision-making

UNIVERSITÀ DEGLI STUDI DI MILANO
LA STATALE

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Antonio Rizzo
Alfredo Santinelli
Cristian Scatena

Thank you!

4oncommunity
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Fabio Pagni
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