

# Predictive Marker Testing in Breast Cancer

## *An Avon Webinar: Patient-Focused Update*

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&

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May 11, 2010

# Goals of This Presentation ...

- Review breast cancer phenotypes
- How predictive markers guide treatment decisions
- The importance of accuracy in predictive biomarker testing
- The critical role of a collaborative multidisciplinary relationship between all health care professionals involved in the care of breast cancer patients

# Characteristics of Good Quality Cancer Care

- Both the patient and disease are treated
- Care is provided in a safe setting
- The right care is offered to the right patient

*(Modified from Vardy and Tannock)*

# What are the Uses for a Tumor Marker?

- Risk of new cancer
- Screening for new cancer
- Differential diagnosis
- Prognosis: primary or metastatic
  - Pure prognosis
  - Prediction
    - Identify who should be offered a specific therapy(ies)  
(or, more importantly, those who should not!)
- Monitoring
  - Ongoing treatment (e.g., preoperative therapy)
  - “NED” for occult recurrence (surveillance)
  - Established metastases

# ER and HER2 have Clinical Utility

- ER+ status is a modest prognostic marker for improved outcome
  - HER2-neg status is a modest to strong prognostic marker
  - However, both are used for therapeutic decision-making as they are strong predictive markers for therapeutic benefit
- *Specially to identify those who are NOT likely to benefit from specific therapies*

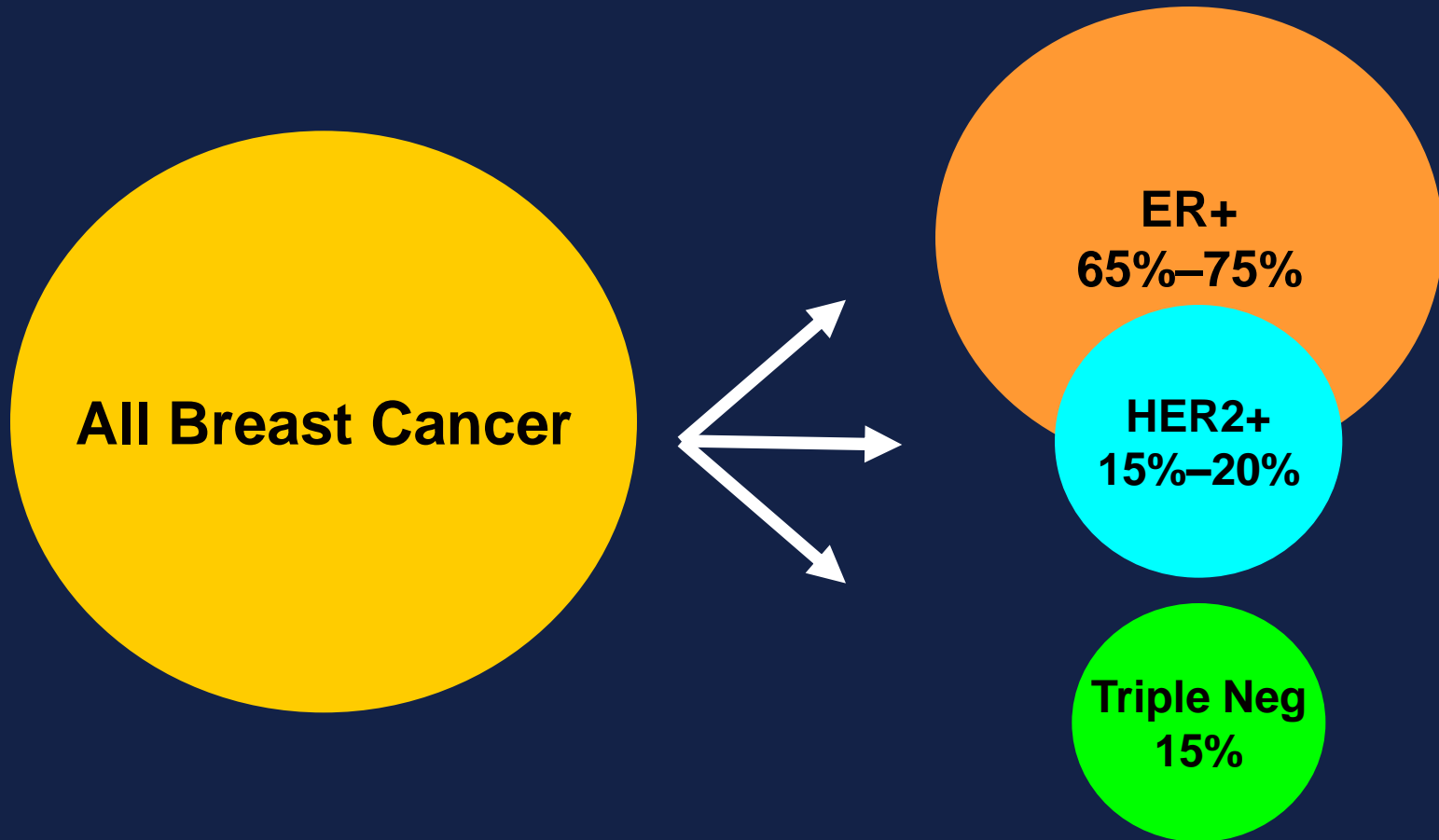
# Endocrine Therapy in Breast Cancer

- Endocrine therapy substantially improves survival in early stage and metastatic disease
- Adjuvant tamoxifen works in patients in all age groups
- Ovarian ablation or suppression is an effective therapy in premenopausal women
- Aromatase inhibitors further improve outcomes when given after a few years of tamoxifen for postmenopausal women diagnosed with early stage breast cancer

# Anti-HER2 Therapy in Breast Cancer

- Anti-HER2 therapy substantially improves survival in early stage and metastatic disease
- Trastuzumab and lapatinib are approved for the treatment of advanced breast cancer
- Trastuzumab substantially improves survival of women diagnosed with HER2-positive early stage breast cancer
  - Lapatinib is now being tested in adjuvant trials
- There are no data to support using anti-HER2 therapy in patients with HER2-negative breast cancer outside of a clinical trial

# Breast Cancer Phenotypes ...



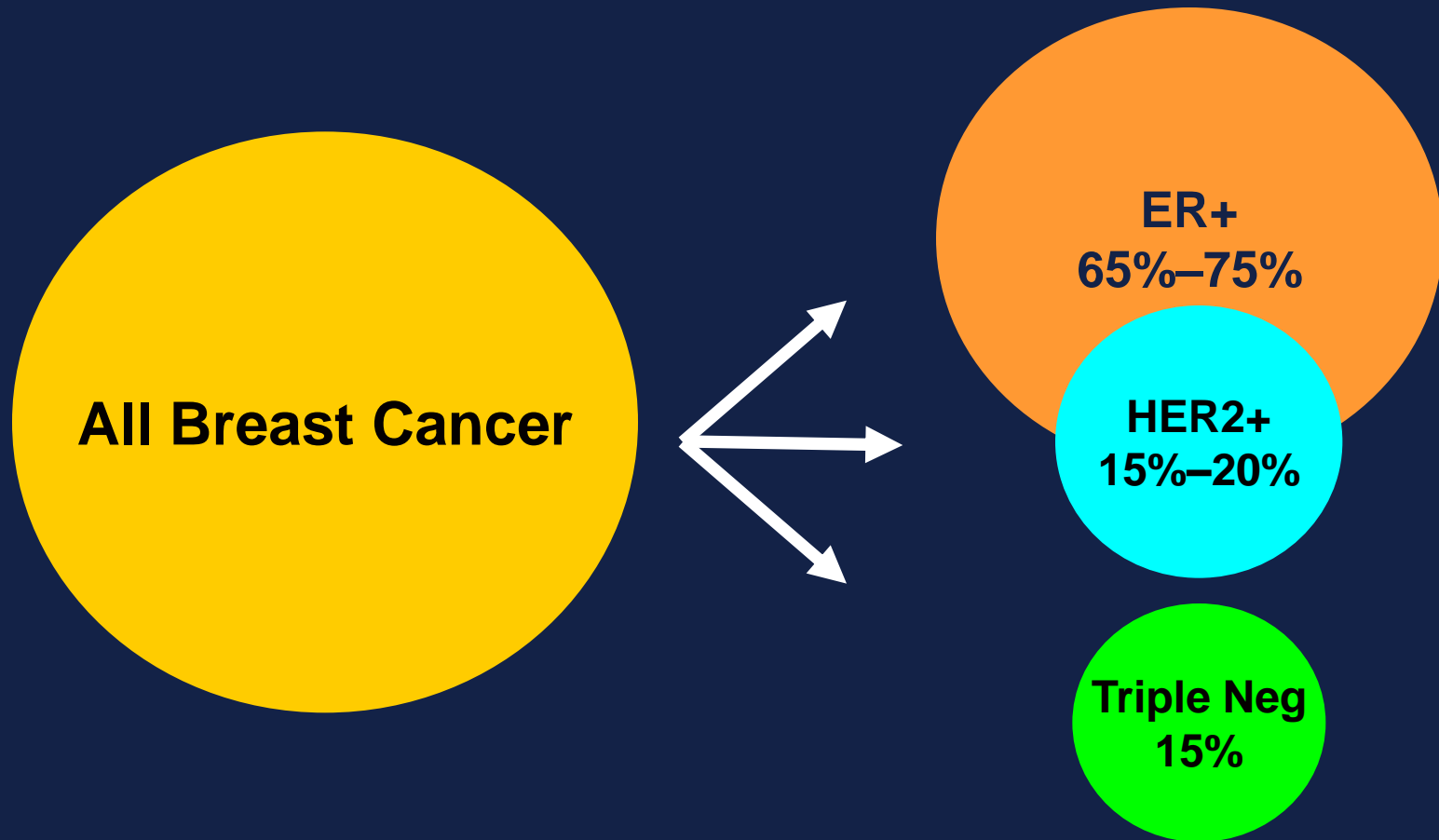
→ Phenotypes of interest for having clear therapeutic implication

# Aim the Target ...

## *St Gallen Consensus Panel 2007*

*“While recognizing the existence of several molecularly-based tools for risk stratification, the Panel preferred to recommend the use of high-quality standard histopathological assessment for both risk allocation and target identification.”*

# Breast Cancer Phenotypes ...



→ Accurate, high-quality predictive marker testing is key to ensure that the right patient receives the right treatment!

# Table 2: Threshold for Rx Modalities

## St Gallen 2009

Treatment Modality	Indication	Comments
Endocrine therapy	Any ER staining <sup>b</sup>	ER-negative, PgR-positive is probably artefactual <sup>73</sup>
Anti-HER2 therapy	ASCO/CAP HER2-positive (>30% intense and complete staining (IHC) or FISH >2.2+) <sup>b</sup>	May use clinical trial definitions
Chemotherapy:		
A. In HER2-pos disease (with anti HER2 therapy)	Trial evidence for trastuzumab is limited to use with or following chemotherapy <sup>b</sup>	Combined endocrine therapy + anti-HER2 therapy without chemotherapy in strongly ER-positive, HER2-positive is logical but unproven
B. In triple neg disease	Most patients <sup>b, c</sup>	No proven alternative. Most at elevated risk
C. In ER-pos, HER2-neg disease (with endocrine Rx)	Variable according to risk <sup>b</sup>	See table 3

*\*Most factors are continuous but a binary decision needs to be made at some level*

# Table 3: Chemoendocrine Rx if ER-pos/HER2-neg

## St Gallen 2009

Clinicopathological Features			
	Relative Indications for Chemoendocrine Rx	Factors Not Useful for Decision	Relative Indications for Endocrine Rx Alone
<b>ER, PgR</b>	Lower ER and PgR level		Higher ER and PgR level
<b>Histological Grade</b>	Grade 3	Grade 2	Grade 1
<b>Proliferation<sup>a</sup></b>	High	Intermediate	Low
<b>Nodes</b>	Node positive (4 or more involved nodes)	Node positive (1-3 involved nodes)	Node negative
<b>Peritumoral Vasc. Invasion (PVI)</b>	Presence of extensive PVI		Absence of extensive PVI
<b>pT-size</b>	> 5cm	2.1 – 5 cm	≤ 2cm
<b>Patient Preference</b>	Use all available treatments		Avoid chemotherapy-related side effects
Multi-gene Assays			
<b>Gene Signature<sup>b</sup></b>	High score	Intermediate score	Low score

# Intrinsic Molecular Classification of Breast Cancer

Intrinsic Subtypes	IHC markers	Proliferation & Grade	Rx Implications
<b>Basal-like</b>	Mostly triple-negative (not always!)	High Ki67, high grade	Worse natural history, quite sensitive to chemo (e.g., preop chemo & pCR)
<b>Luminal A</b>	Mostly ER+	Low Ki67, low grade	Indolent, sensitive to endocrine Rx
<b>Luminal B</b>	Mostly ER+	Often high Ki67, high grade	Less/insensitive to endocrine Rx, more sensitive to chemo
<b>HER2+</b>	HER2 over expressed	High Ki67	Worse natural history, quite sensitive to anti- HER2 Rx

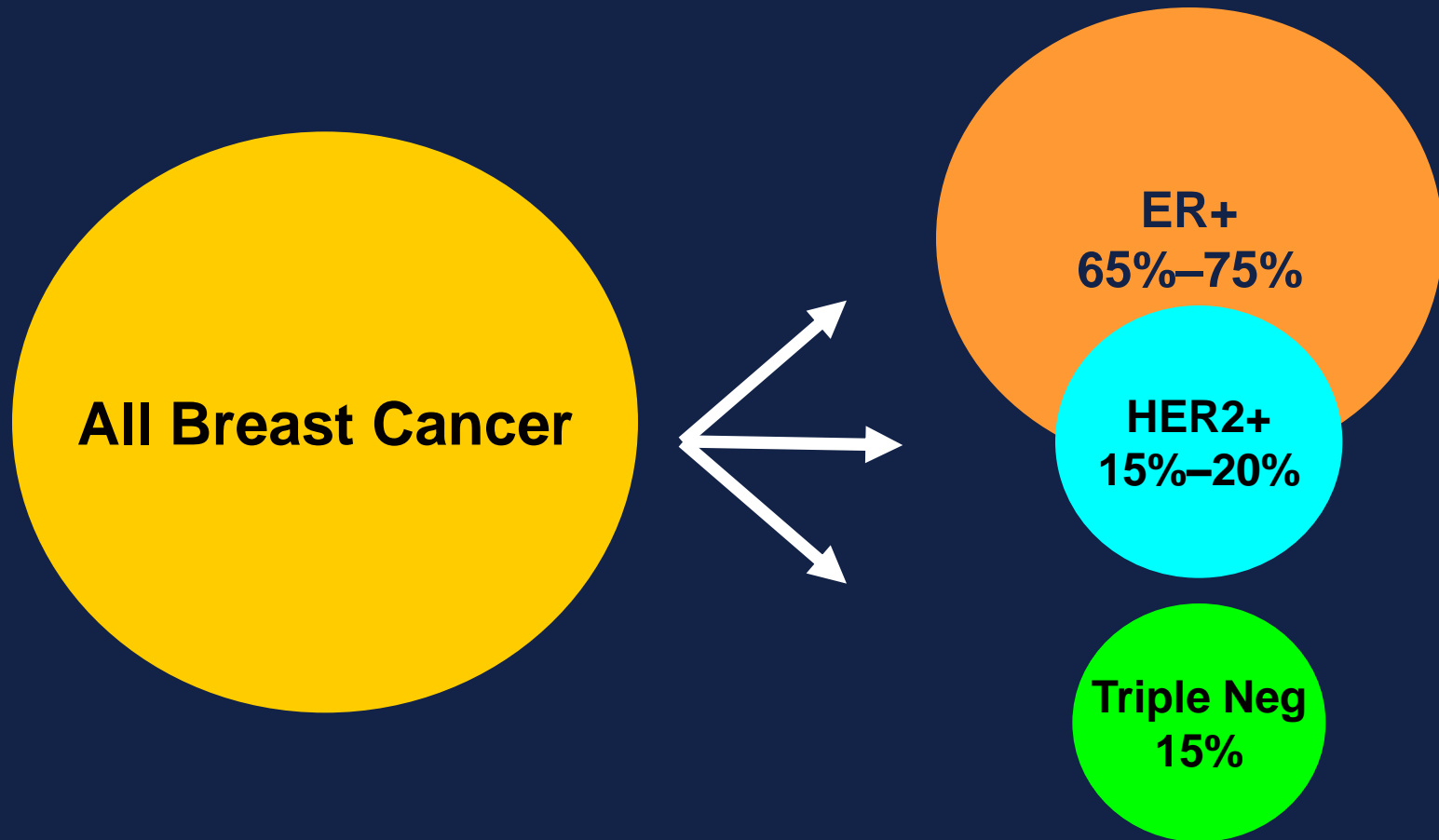
# Aim the Target ...

## *St Gallen Consensus Panel 2009*

*“The Panel agreed that **validated multi-gene tests**, if readily available, **could assist in deciding whether to add chemotherapy in cases where its use was uncertain after consideration of conventional markers.**”*

*“First generation **genetic signatures contain genes sampling the ER, HER2 and proliferative pathways.** Meta-analysis suggests that **much of the prognostic information in these signatures resides in their sampling of proliferative genes.**”*

# Breast Cancer Phenotypes ...



→ *Accurate, high-quality predictive marker testing is key to ensure that the right patient receives the right treatment!*

# ER Concordance for IHC Local vs Central Testing

ECOG 2197	ER Central (ECOG Path Coord Office)		
ER Local (institutional criteria)	Positive (Allred score $\geq 3$ )	Negative	Total
Positive	382	27 (FP 8%)	409
Negative	48 (FN 11%)	312	360
	430	339	769
Overall Concordance	90% (95% CI, 88-92%)		

# ER Concordance for IHC Local vs Central Testing

ALTTO Trial	ER Central (European Institute of Oncology)			
	Positive (≥ 10%)	Positive (1% to 9%)	Negative	Total
Positive	2481	54	113 (FP 4.3%)	2,648
Negative	388 (FN 16.9%)	107 (FN 4.7%)	1,788	2,283
	2,869	161	1,901	4,931

# HER2 Testing Concordance in N9831

## Concordance Central vs Local Lab

	JNCI 2002 (total n = 119)	ASCO 2004 (total n = 976)	JCO 2006 (total n = 2535)
IHC 3+ (HercepTest)	74%	79.5%	82% <i>(false pos 18%)</i>
FISH + (PathVysion)	67%	85%	88% <i>(false pos 12%)</i>

# Sources of Testing Variation

## Preanalytic

- Time to fixation
- Method of tissue processing
- Time of fixation
- Type of fixation

## Analytic

- Assay validation
- Equipment calibration
- Use of standardized laboratory procedures
- Training and competency assessment of staff
- Type of antigen retrieval
- Test reagents
- Use of standardized control materials
- Use of automated laboratory methods

## Postanalytic

- Interpretation criteria
- Use of image analysis
- Reporting elements
- Quality assurance procedures
  - Laboratory accreditation
  - Proficiency testing
  - Pathologist competency assessment

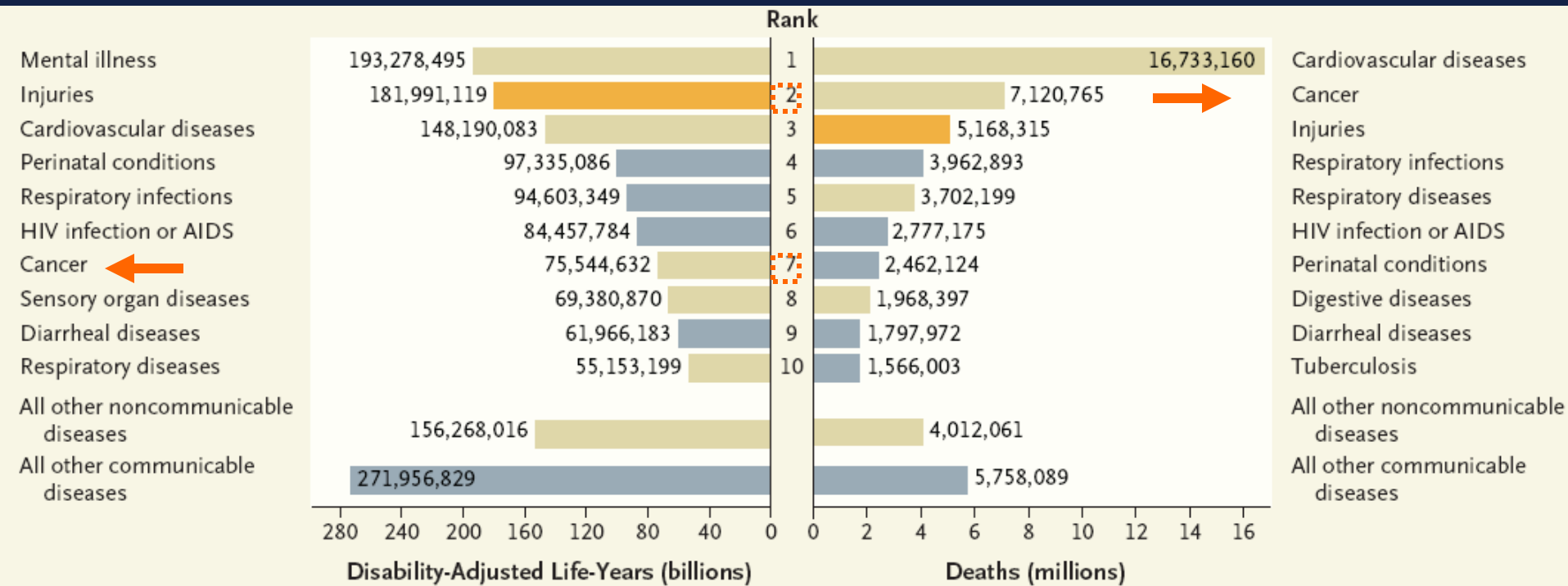
# Myth #1

- *“Cancer is an insignificant health care issue in low and middle income countries (LMCs)”*

**FACT:** Cancer is the second most common cause of death in LMCs, more than respiratory infections and diseases, HIV/AIDS, diarrhea diseases, and tuberculosis

# Confronting Chronic Disease in Countries with Low Income: Myths in Play ...

## *Major Diseases and Conditions in the World*

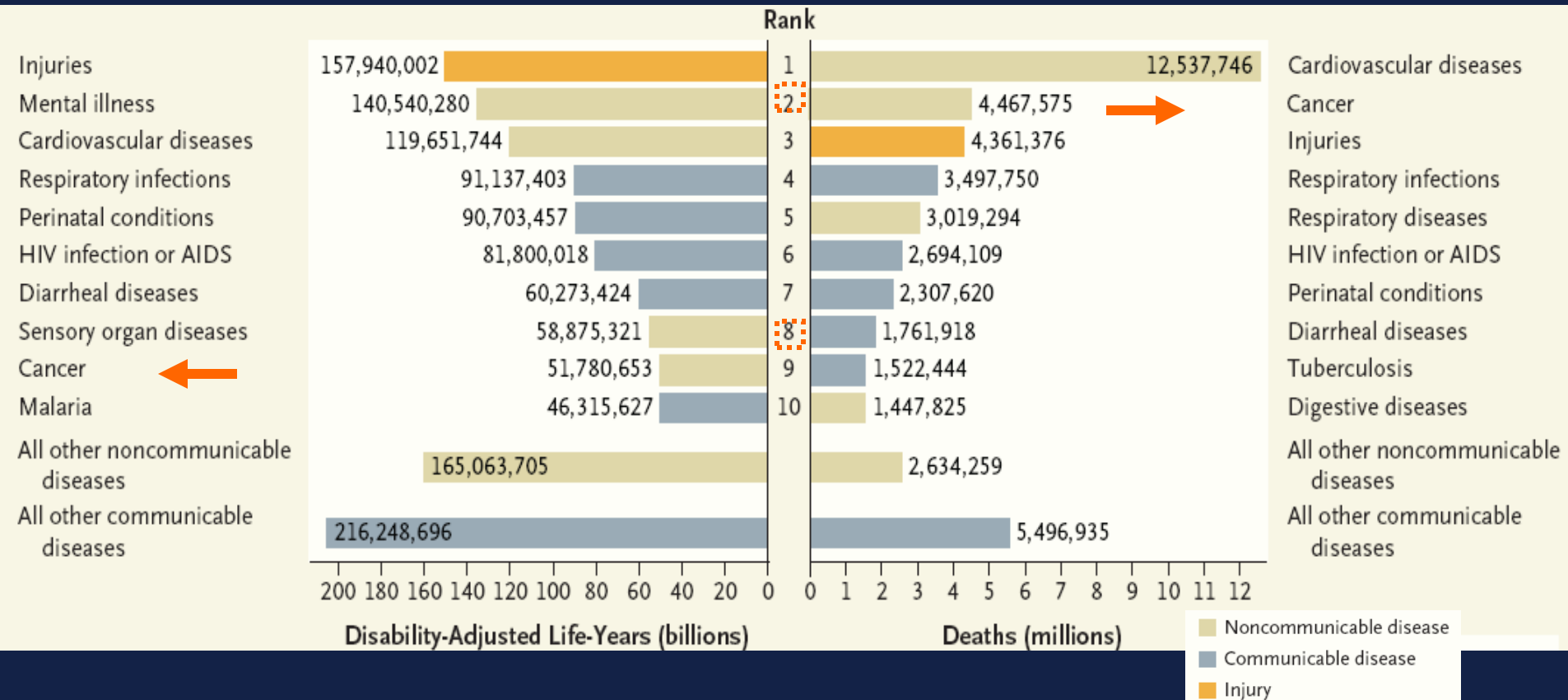


■ Noncommunicable disease  
■ Communicable disease  
■ Injury

Years of Healthy Life Lost (Disability-Adjusted Life-Years) and Deaths According to Disease or Condition. Perinatal conditions include low birthweight, prematurity, birth asphyxia, and birth trauma. Data are from the World Health Organization.

# Confronting Chronic Disease in Countries with Low Income: Myths in Play ...

## Major Diseases and Conditions in Low- & Lower-Middle Income Countries



Years of Healthy Life Lost (Disability-Adjusted Life-Years) and Deaths According to Disease or Condition.

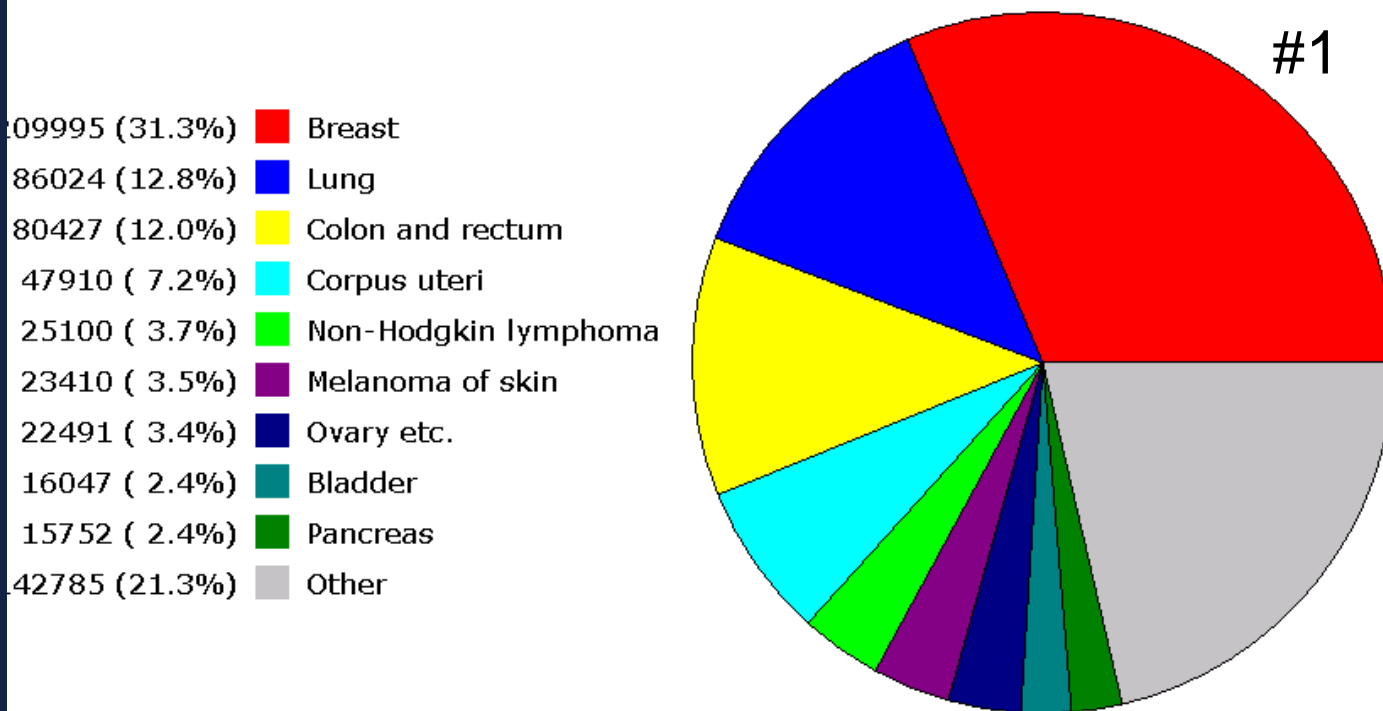
Perinatal conditions include low birthweight, prematurity, birth asphyxia, and birth trauma. Data are from the World Health Organization.

# Myth #2

- *“Breast cancer only affects wealthy countries”*

**FACT:** Breast cancer is the most common cancer among women worldwide, and the most likely reason that a woman will die of cancer

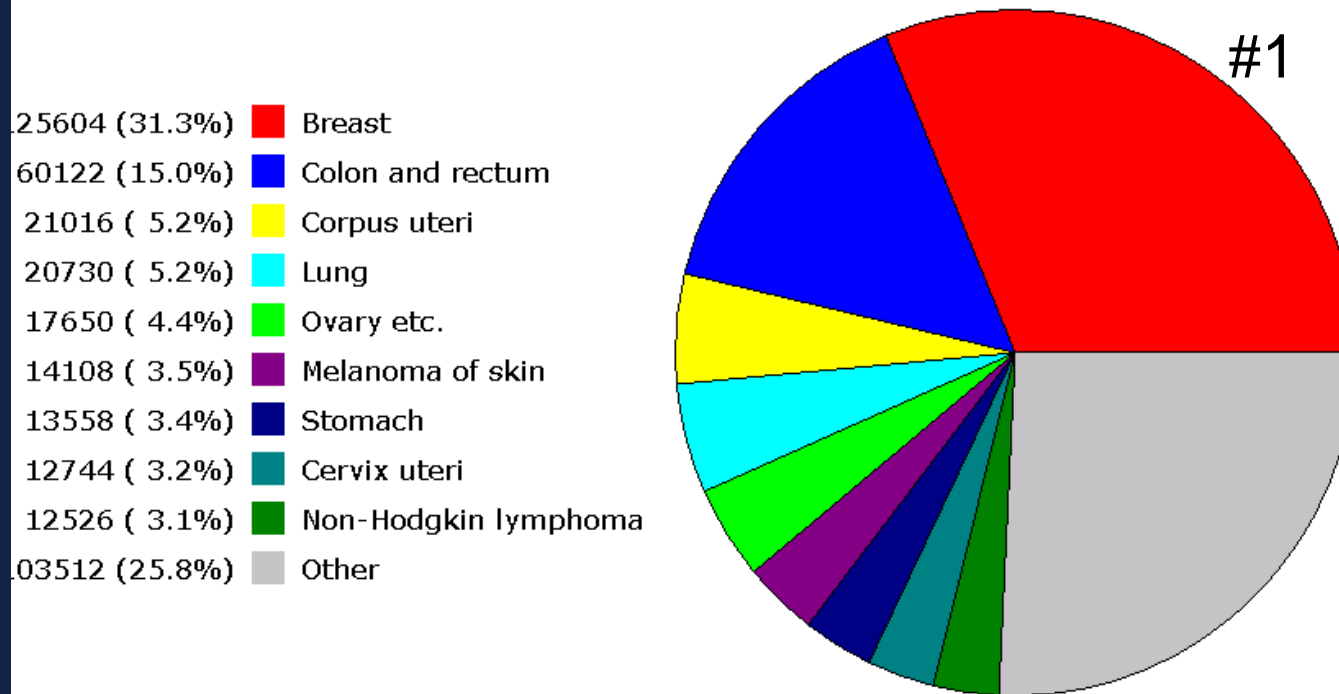
United States of America  
New cancer cases (all ages), Females  
Total: 669941



GLOBOCAN 2002, IARC

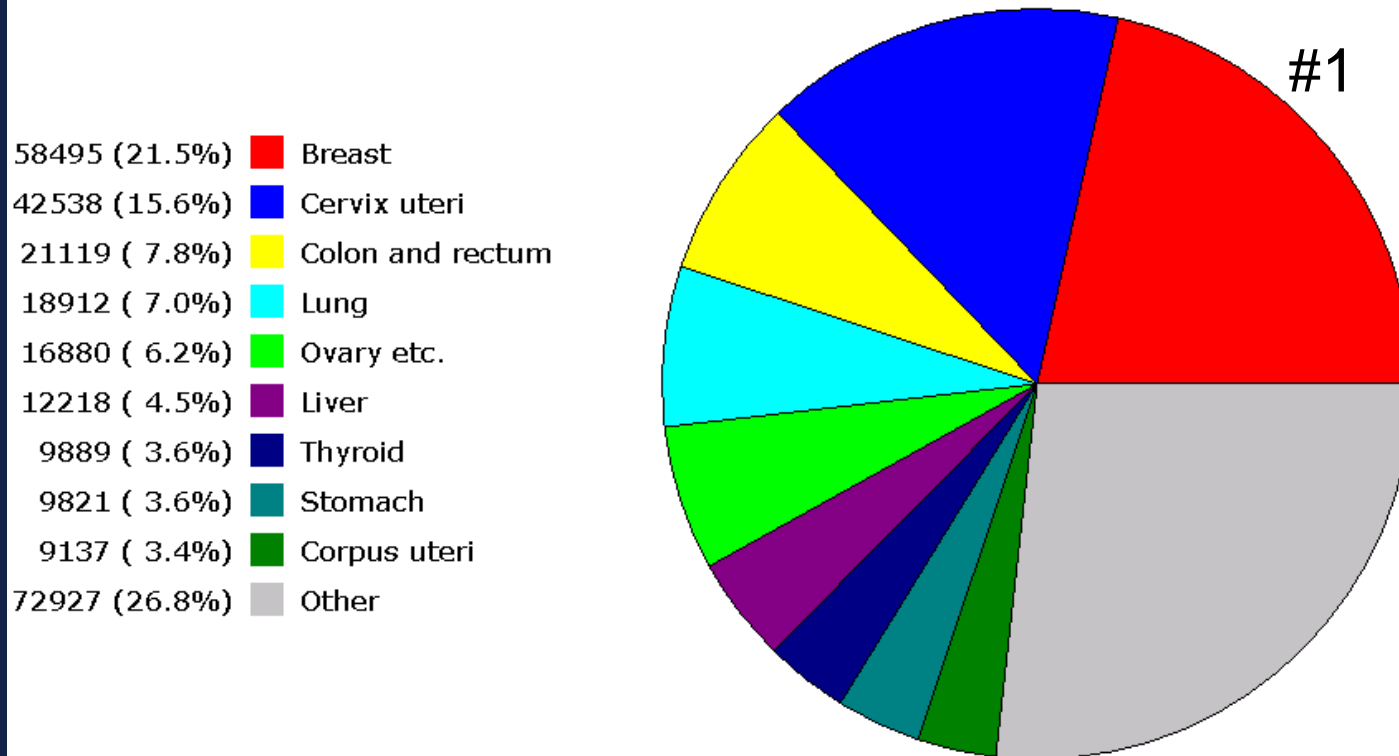
[www-dep.iarc.fr](http://www-dep.iarc.fr)

Western Europe  
New cancer cases (all ages), Females  
Total: 401570



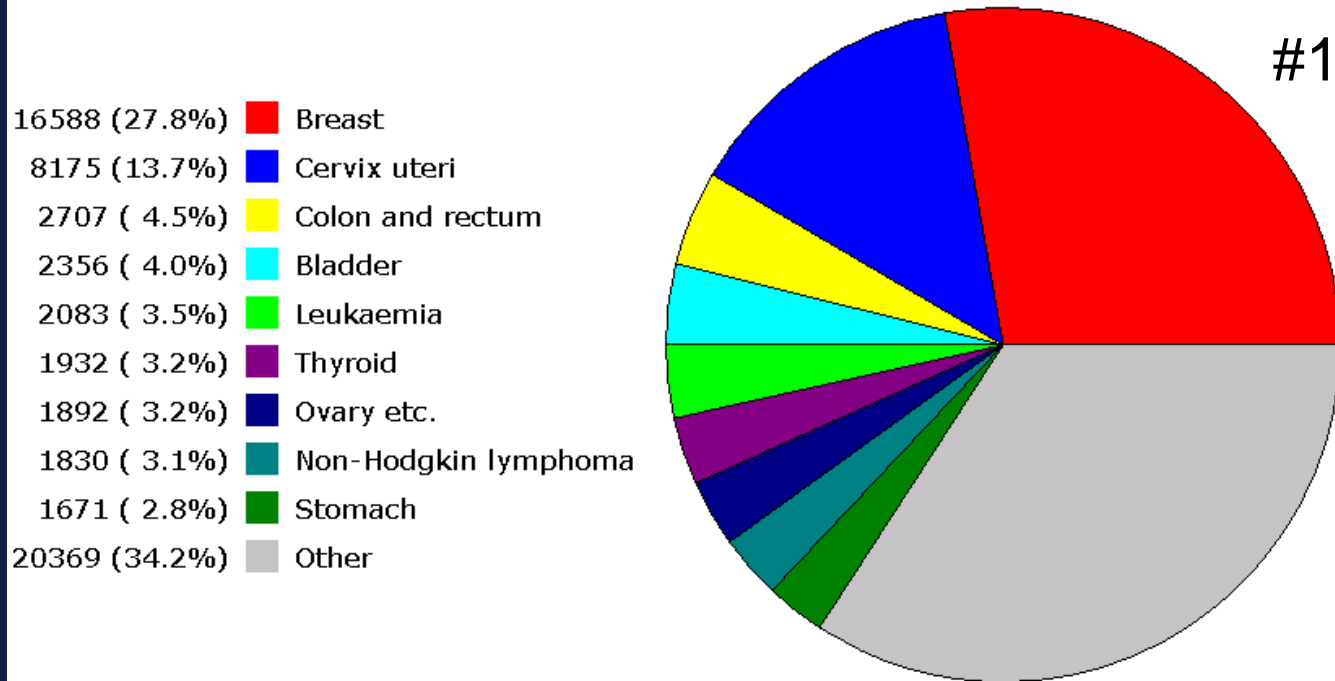
GLOBOCAN 2002, IARC

South-Eastern Asia  
New cancer cases (all ages), Females  
Total: 271936



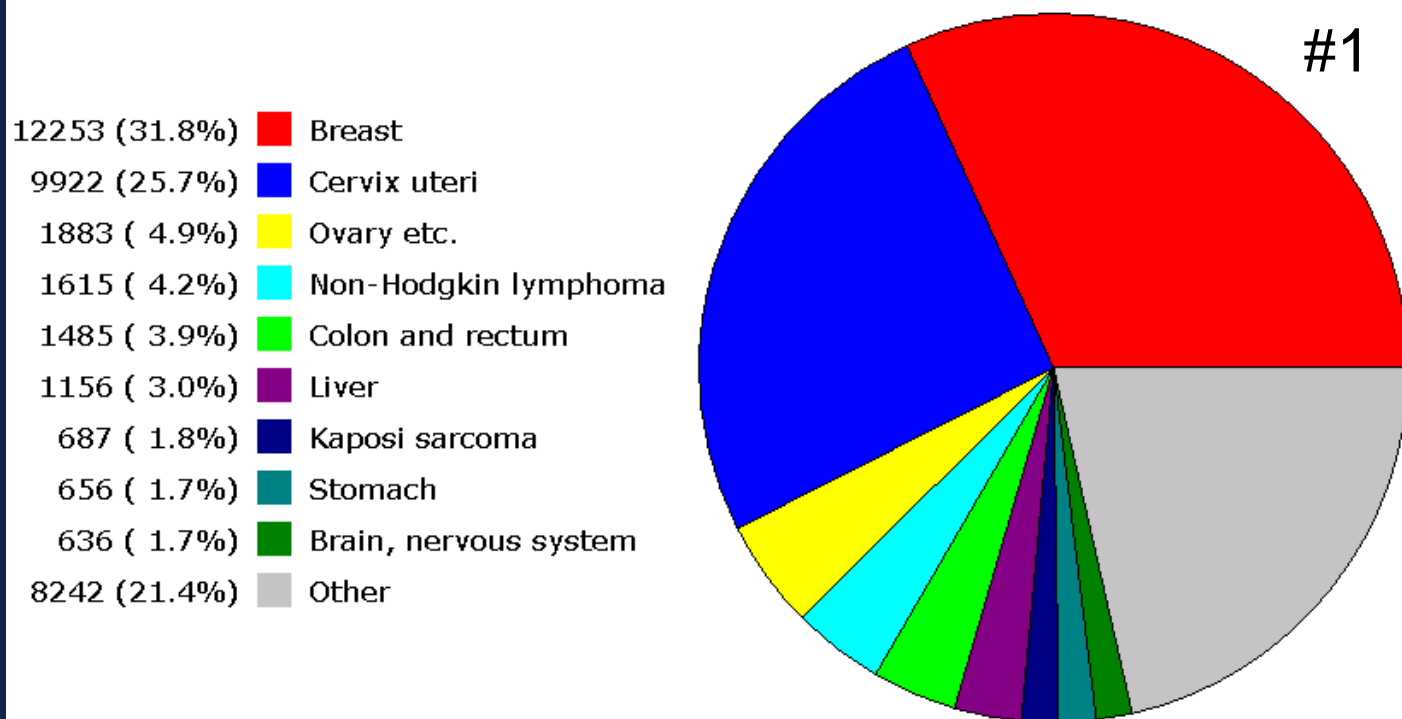
GLOBOCAN 2002, IARC

Northern Africa  
New cancer cases (all ages), Females  
Total: 59603



GLOBOCAN 2002, IARC

Nigeria  
New cancer cases (all ages), Females  
Total: 38535




## Myth #3

- *“Breast cancer in low and middle income countries (LMCs) is more likely to have an ER-negative phenotype”*

**FACT:** Cancers in LMCs appear to have a similar phenotype profile when compared to breast cancers diagnosed in wealthier countries

# Prevalence of ER-pos Disease in LMCs

	Philippines (Gemma et al, PJSS 2007)		Vietnam/ China (Nichols et al, CEBP 2005)	Malaysia (Tan & Yip, oral communication)	Nigeria (Adebamowo et al, BCRT 2007)
n (year)	638 (2003-5)	362 (2006)	682 (1993-1999)	996 (2005-2007)	192 (2004-2006)
Age (range)	52% > age 50		median 41 (24-57)	mean 53.3 (87% > age 40)	mean 49.5 (27-74)
ER and/ or PR+	59.4%  68.9%		61% ER+	61%	65% ER+ 58% PgR+
HER2+	-		35%	30%	20%
<i>Comments</i>	<i>Before and after standardization of specimen retrieval</i>		<i>All premenopausal</i>	<i>Triple neg 18%</i>	

Volume 25 \* Number 1 \* January 1 2007

JOURNAL OF CLINICAL ONCOLOGY

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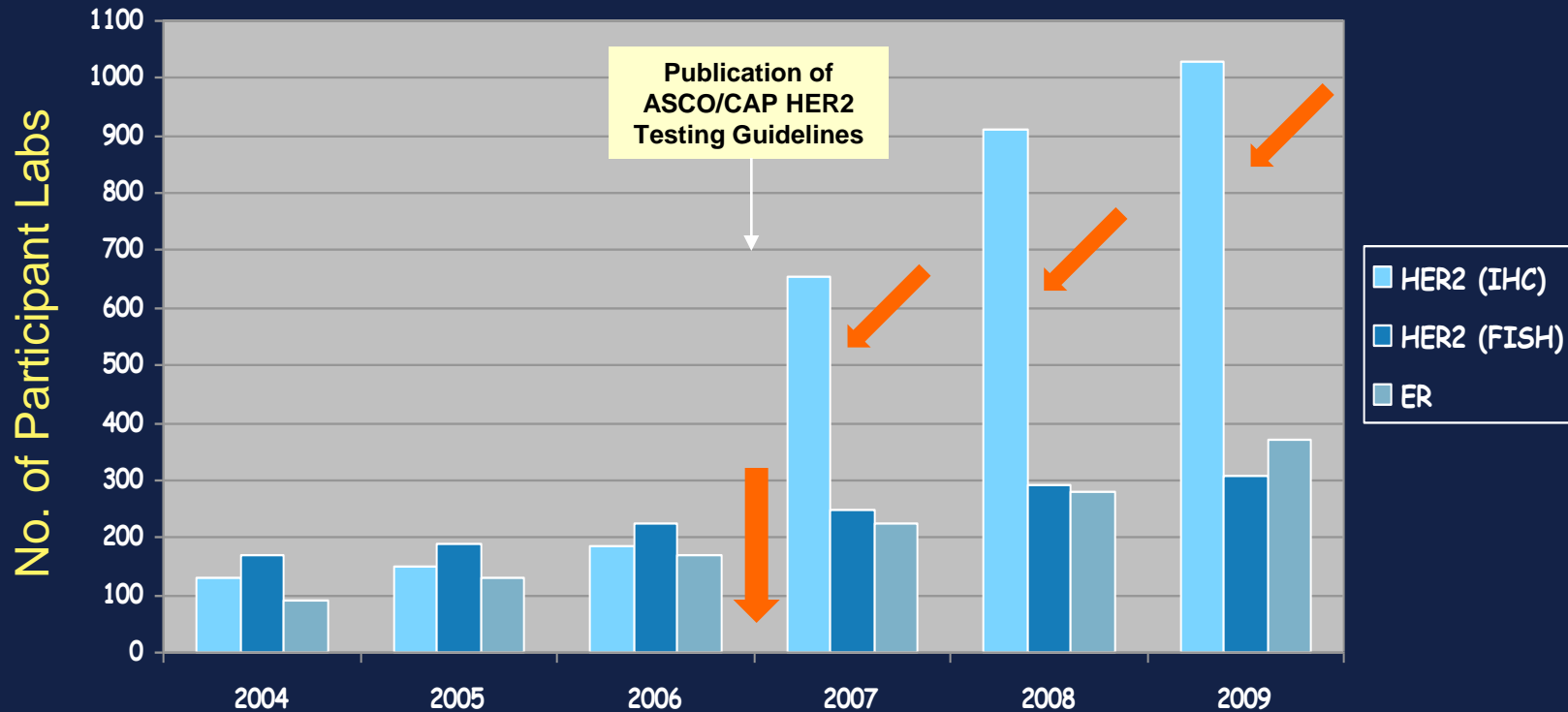
Pathology &  
Laboratory Medicine

# American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

*Antonio C. Wolff\*, M. Elizabeth H. Hammond\*, Jared N. Schwartz\*, Karen L. Hagerty, D. Craig Allred, Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila E. Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler, Daniel F. Hayes\**

→ 2<sup>nd</sup> most downloaded JCO paper in 2007 ...

# CAP Survey Enrollment



## Concordance Central vs Local Lab

	JNCI 2002 (total n = 119)	ASCO 2004 (total n = 976)	JCO 2006 (total n = 2535)
IHC 3+ (HercepTest)	74%	79.5%	82% <i>(false pos 18%)</i>
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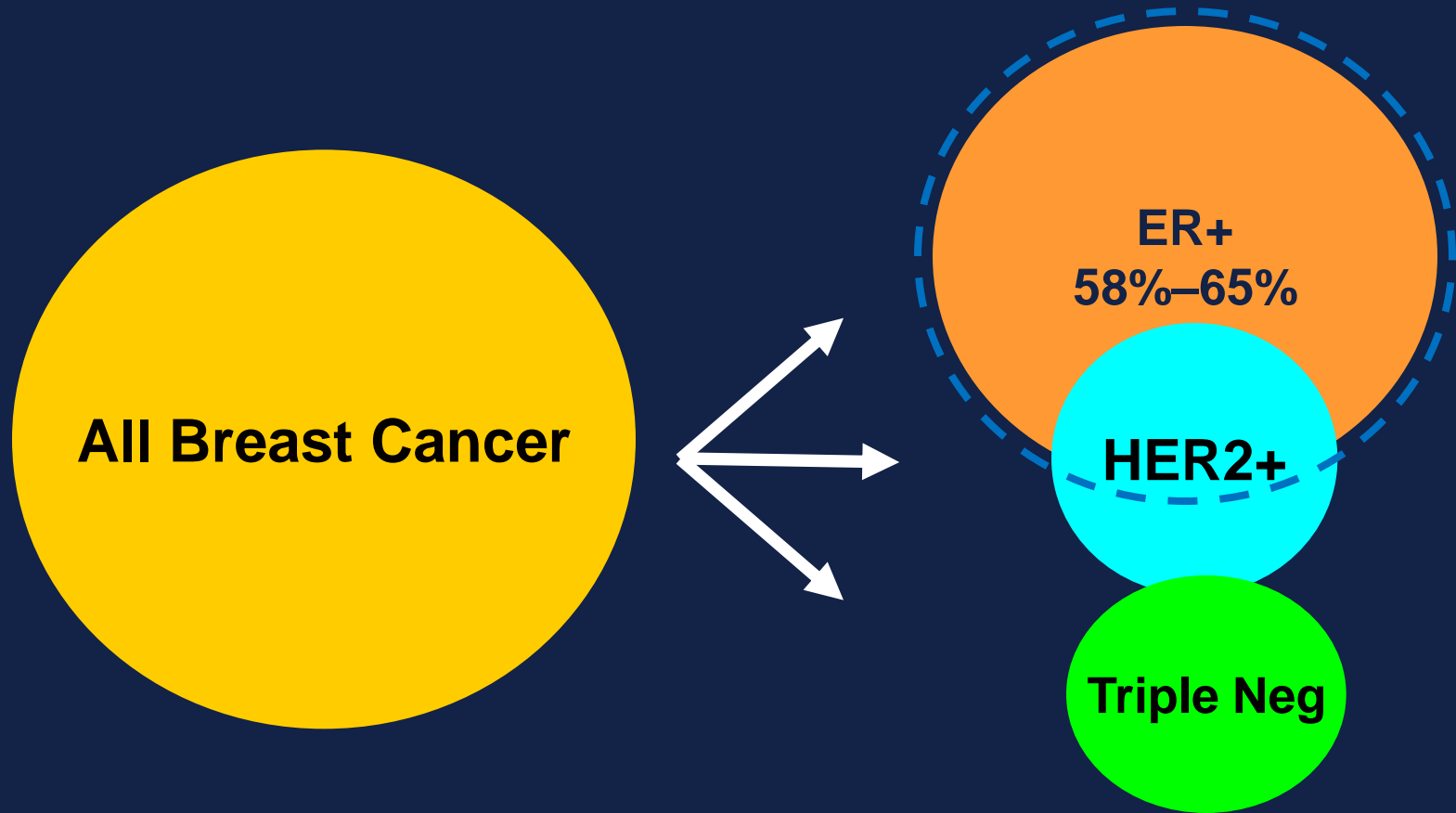
FutureData

→ ??

→ ??

# Hormone Receptor Testing

## *A Global Population Health Issue!*



- Endocrine therapy (TAM, oophorectomy) is “affordable” ...
- High quality ER/PgR testing is possible ...

Published online – April 19, 2010

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

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Pathology &  
Laboratory Medicine

# American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

*M. Elizabeth H. Hammond\*, Daniel F. Hayes\*, Mitch Dowsett\*, D. Craig Allred\*, Karen L. Hagerty, Sunil Badve, Patrick L. Fitzgibbons, Glenn Francis, Neil S. Goldstein, Malcolm Hayes, David G. Hicks, Susan Lester, Richard Love, Pamela B. Mangu, Lisa McShane, Keith Miller, C. Kent Osborne, Soonmyung Paik, Jane Perlmutter, Anthony Rhodes, Hironobu Sasano, Jared N. Schwartz, Fred C.G. Sweep, Sheila Taube, Emina Emilia Torlakovic, Paul Valenstein, Giuseppe Viale, Daniel Visscher, Thomas Wheeler, R. Bruce Williams, James L. Wittliff, and Antonio C. Wolff\**

→ *Stakes are potentially much higher this time ...*

# Take Home Messages ...

- Breast cancer phenotypes matter
- Accuracy in predictive markers testing is critical to ensure that the right patient receives the right treatment
- It takes a village to take care of biospecimens used for predictive biomarker testing, from the moment they leave a patient's body to the final report of test assay

M. Elizabeth H. Hammond, MD, FCAP  
Intermountain Healthcare and  
University of Utah

# HER2 and ER/PgR Testing Variation

- Accurate HER2 and ER/PgR tests (predictive markers) are key to ensuring that patients are offered the most effective treatment for breast cancer
- Through publications and other evidence we learned that this testing was variable
- The guidelines were developed to control testing variation and thereby improve accuracy of testing for patients with breast cancer

# Laboratory Reality: HER2 and ER/PgR Testing Not Accurate in High Percentage of Cases

- Some HER2 protein expression tests were called positive when they were not
- Some HER2 FISH assays were also variable
- Several studies confirm that ER and PgR testing by IHC varied from **5-20%**, mostly false negatives
- False positive results mean that that patient may have received therapy, but perhaps should not have
- False negative results mean that a patient should have had the opportunity to receive a therapy but did not

*Source: Comparative studies of National Clinical Trial Groups with Institutional Pathologist Performance (NSABP and Intergroup Studies)*

# What Can be Done to Control Variation in Predictive Factor Assays?

**Design Work So That  
It Is Easy To Do It Right  
And Hard To Do It Wrong**

**The National Forum For Health Care  
Quality Measurement And Reporting**

# Guidelines to Control Testing Variation

- Standardize specimen handling for breast cancer specimens
- Clearly define acceptable testing conditions
- Specify how test results should be reported
- Define quality laboratory monitoring process

# Relationship of HER2 and ER/PgR Guidelines

- **Format of each guideline similar**
  - Define positive, negative, equivocal
  - Specimen Handling Considerations
  - Testing parameters
  - Reporting requirements
  - QA requirements
- **Each guideline is living document which will be modified when there is new evidence**

# Specimen Handling

When the tumor is removed from the patient, the specimen starts to degrade and it is more difficult to get an accurate HER2 or ER/PgR result.

- Time from tumor excision to the time the specimen is delivered to the lab should be as short as possible (<1 hour)
- Time of removal from patient and time specimen placed in formalin **must be recorded\***
- A specific fixative (10% Neutral buffered formalin) must be used as fixative. Fixative **must be recorded**
- Fixation time must be >6 hours and <72 hours and **must be recorded\***
- Remotely obtained samples **should be bisected** and placed in formalin before shipping to central site.\*
- Slides for testing should not be stored longer than 6 weeks

# Testing Conditions

- Laboratory should use **FDA-approved kits** for the testing of HER2 if possible
- Automated testing platforms are preferred
- **Controls** must be run with each batch and, ideally, on each slide
- If ER testing is found to be negative, a retest may be needed
- Each Guideline defines others specifics

# Testing Parameters HER2

- Laboratory should use **FDA-approved kits** for the testing if possible
- Automated testing platforms are preferred
- **Controls** must be run with each batch and ideally on each slide
- Image analysis is desirable for quantifying result
- Laboratory must **maintain 95% concordance** between HER2 IHC and FISH to know when tests should be sent for the complementary test

# Testing Parameters ER/PgR

- Laboratory should only use **antibodies reported to have clinical utility** in predicting patients who will respond to hormonal based therapy.
- Automated testing platforms are preferred
- Controls must be run with each batch and ideally on each slide
- Image analysis is desirable for quantifying result
- Negative ER/PgR results may need retesting depending on assay conditions/sample issues

# Reporting Requirements HER2 and ER/PgR

- Patient demographics
- Specifics of specimen used for testing
- Details of controls/testing procedure (either in report or on file)
- Statement about whether elements for each guideline have been met
  - Specimen handling considerations
  - Controls used and evaluated
  - Testing inclusion/exclusion criteria/adequacy

# Optimal Testing Algorithm HER2 IHC

Breast cancer specimen (invasive component)

HER2 testing by validated IHC assay for HER2 protein expression

Positive for HER2 protein expression IHC 3+ (defined as uniform intense membrane staining of >30% of invasive tumor cells)

Negative for HER2 protein expression IHC 0 or 1+

Equivocal for HER2 protein expression IHC 2+

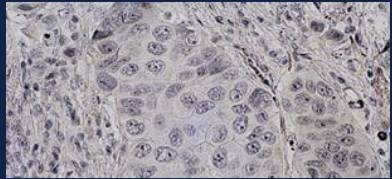
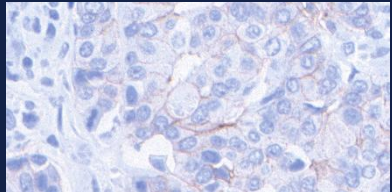
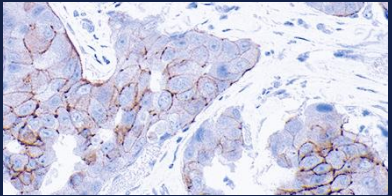
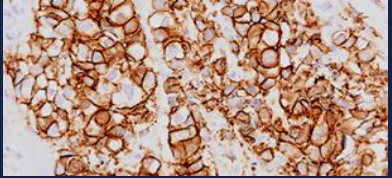
Test with validated assay for *HER2* gene amplification

Positive for *HER2* gene amplification

Equivocal *HER2* gene amplification (Patients with *HER2*/CEP17 ratio  $\geq 2.0$  were eligible for the adjuvant trastuzumab trials)

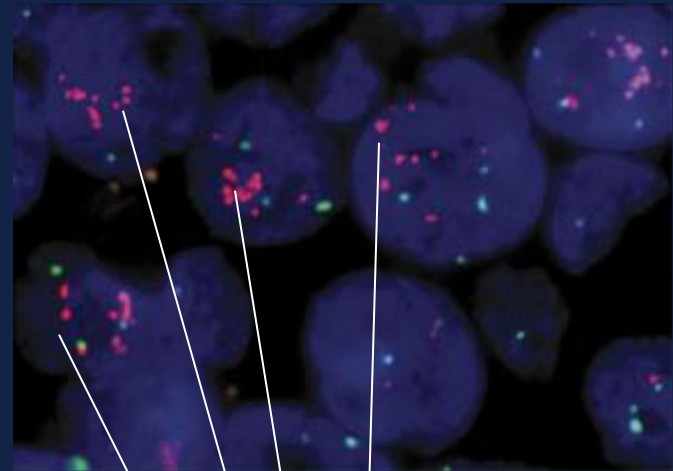
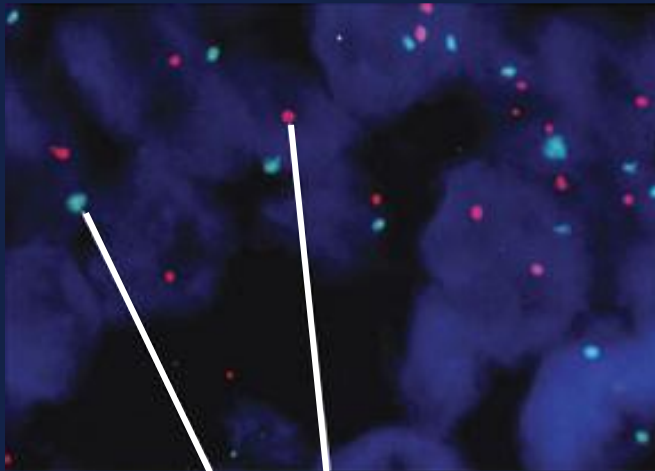
Negative for *HER2* gene amplification

# Interpretation of HER2 Overexpression

Staining Pattern	Score	HER2 Overexpression Assessment	Example Stain
No staining is observed or membrane staining is observed in less than 10% of the tumor cells.	0	Negative	
Partial membrane staining of any intensity is seen in more than 10% of the tumor cells. The cells are only stained in part of their membrane.	1+	Negative	
A weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.	2+	Equivocal	
A strong complete membrane staining is observed in more than 10% of the tumor cells.	3+	Positive	

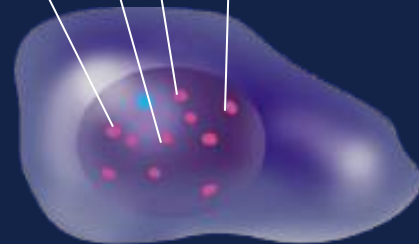
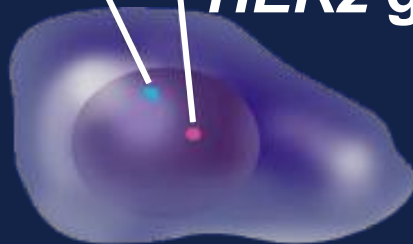
# FISH Test Quantitatively Measures *HER2* Gene Amplification

Count and average gene signals in tumor cell nuclei



Chromosome 17  
centromere

*HER2* gene



***HER2* normal ratio < 2.0 *HER2* amplified ratio > 2.0**

*Pauletti et al, Oncogene 1996; Pauletti et al, J Clin Oncol 2000; Press et al, J Clin Oncol 1997; Sjogren et al, J Clin Oncol 1998; Sliwkowski et al, Semin Oncol 1999*

# Interpretation of HER2

Result Category	Testing Method	
	<u>IHC Score</u> HER2 Protein Expression	<u>FISH Score</u> <i>HER2</i> Gene Amplification
Positive	3+**	<i>HER2</i> /CEP 17 ratio >2.2 or Average <i>HER2</i> gene copy number >6 <sup>§</sup>
Equivocal	2+	<i>HER2</i> /CEP 17 ratio of 1.8 – 2.2 or Average <i>HER2</i> gene copy number 4 – 6 <sup>§</sup>
Negative	0 – 1+	<i>HER2</i> /CEP 17 ratio <1.8 or Average <i>HER2</i> gene copy number <4 <sup>§</sup>

\*\* Defined as uniform intense membrane staining of >30% of invasive tumor cells

<sup>§</sup> Signals/nucleus for those test systems without an internal central probe

# Optimal Testing Algorithm

## HER2 FISH

Breast cancer specimen (invasive component)

HER2 testing by validated FISH assay for *HER2* gene amplification

Positive for *HER2* gene amplification (FISH ratio  $>2.2$  or *HER2* gene copy  $>6.0$ )

Equivocal for *HER2* gene amplification (FISH ratio 1.8-2.2 or *HER2* gene copy 4.0-6.0)

Negative for *HER2* gene amplification (FISH ratio  $<1.8$  or *HER2* gene copy  $<4.0$ )

Count additional cells for FISH or retest, or test with *HER2* IHC

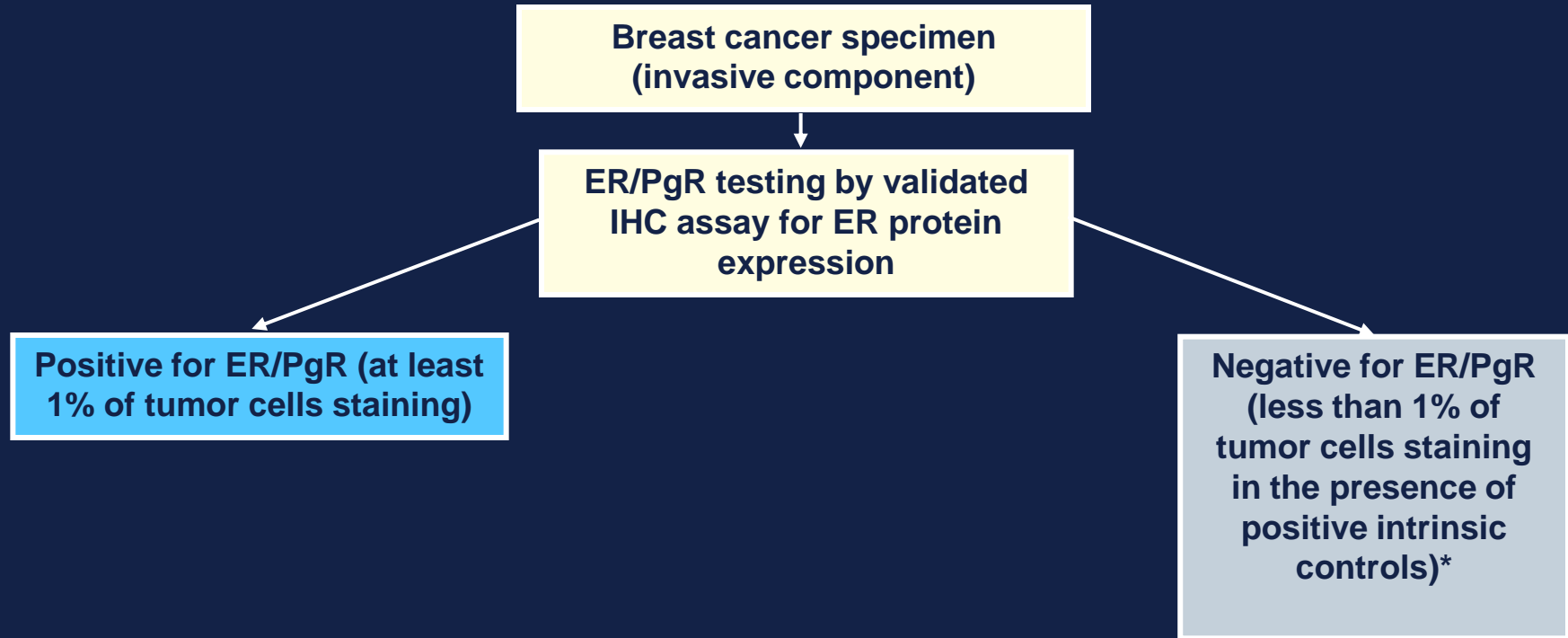
Equivocal *HER2* gene amplification result (Patients with *HER2*/CEP17 ratio  $\geq 2.0$  were eligible for the adjuvant trastuzumab trials)

# Interpretation of ER/PgR

## Interpretation

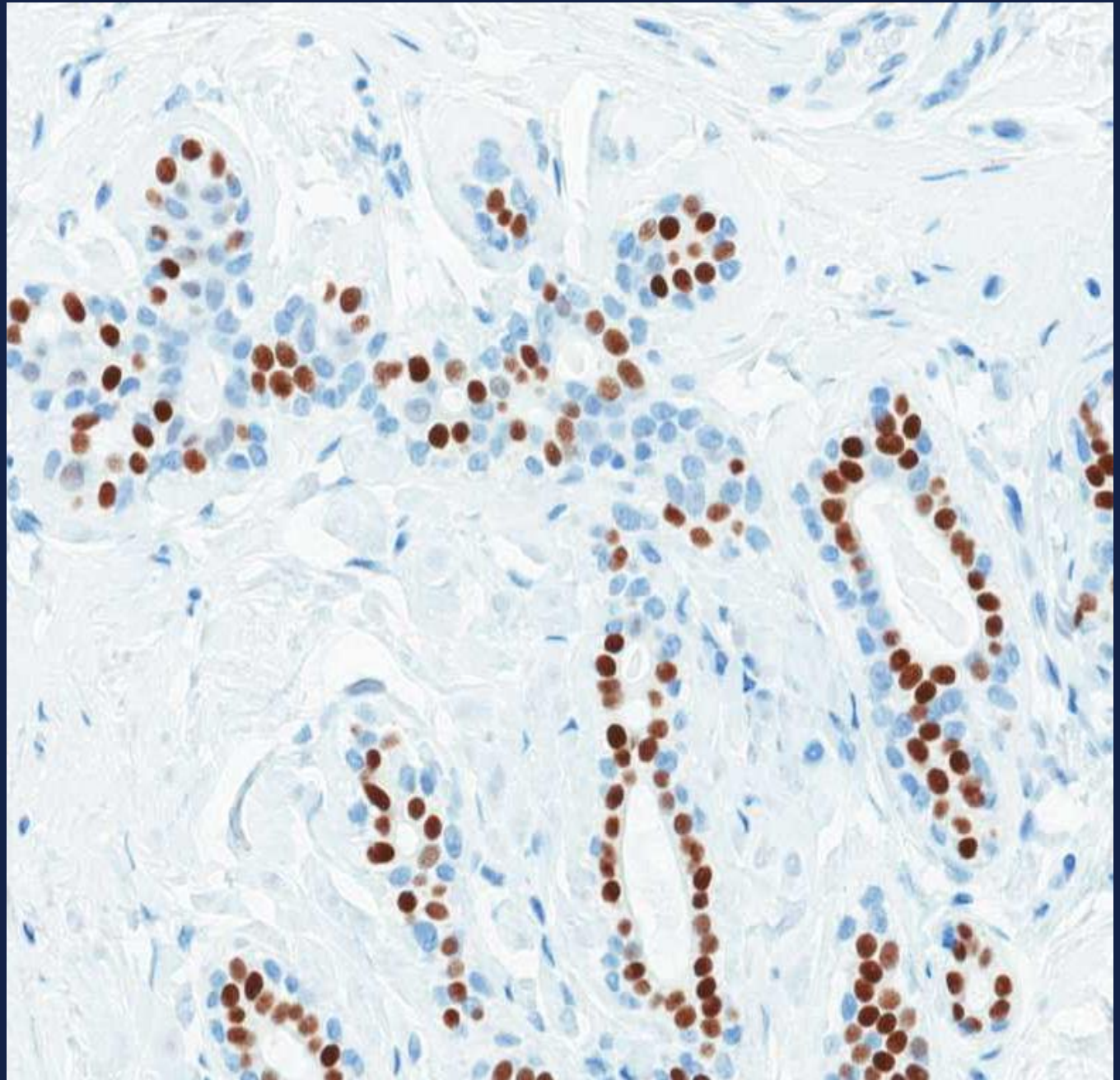
- **Positive:** 1% or more of invasive tumor cells show nuclear ER/PgR of any intensity
- **Negative:** less than 1% of invasive tumor cells show nuclear ER/PgR in presence of adequate controls
- The threshold of 1% is very important to the
- correct interpretation of positive for ER or PgR

# ASCO/CAP ER/PgR Algorithm



**\* = Negative results in grade 1 tumors should be reported as negative ONLY in the presence of intrinsic positive controls**

ER positive  
invasive tumor  
focus  
All cells are  
not positive



Negative ER in high grade  
Tumor lacking internal controls



# Laboratory Quality Assurance and Accreditation

- Laboratories must follow the QA elements of CLIA '88, a federal law defining laboratory QA
  - Initial testing validation must be done before a lab may offer the test
  - Standard operating procedures must be followed
  - Testing personnel must be trained and their competency assessed
  - The testing procedure needs to be monitored and the lab must enroll in proficiency testing
  - The Laboratory must be accredited by the appropriate agency
    - The CAP, JC, and NY State are deemed agencies
    - On site inspection occurs every other year

# Summary

- Guideline elements for HER2 and ER/PgR are very similar
- Elements were created to decrease testing variation
- Guidelines are living evidence-based documents that will be modified when new evidence becomes available
- Guidelines will ensure accurate testing for breast cancer patients around the world

# Acknowledgements:

## Our Co-ASCO/CAP Hormone Receptor & HER2 Testing Collaborations

- Co-chair, Dan F. Hayes, MD (University of Michigan)
- D. Craig Allred, MD, FCAP, and Mitch Dowsett, MD (Steering Committee, Hormone Receptor Testing Panel)
- All panel members (*including Jared Schwartz, MD, FCAP, former panel co-chair*)
- ASCO and CAP Staff (*special thanks to Karen Hagerty and Pamela Mangu*)
- ASCO/Cancer Care Ontario ER testing systematic review collaboration

# *Thank you ...*

## References:

- ASCO/CAP press release → [tinyurl.com/y4zx8wx](https://tinyurl.com/y4zx8wx)
- Letter to the NYT Editor → [tinyurl.com/2856odm](https://tinyurl.com/2856odm)
- Patient web sites → [cancer.net](https://cancer.net) & [mybiopsy.org](https://mybiopsy.org)

*Extra Slides*

April 19, 2010

# ASCO/CAP Guideline Recommendation for IHC Testing of ER/PgR in Breast Cancer

## Press Release

“The ASCO/CAP Panel chose to specifically focus on IHC assays for ER/PgR testing based on its widespread use, worldwide impact, and large body of evidence available. In the future, the ASCO/CAP Panel may review new methods and predictive assays to identify patients most likely to benefit from endocrine therapies as new high-level data on validated assays and outcomes become available.

“All medical professionals involved in cancer care want to do the right thing and offer the most correct and appropriate care to their patients. It is our hope that the ASCO/CAP ER/PgR guideline will facilitate processes at each health system and institution, so that appropriate measures to ensure accurate predictive biomarker testing (including ER/PgR) are in place and that breast cancer patients receive the highest quality care possible,” said Dr. Hammond.”

April 19, 2010

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“The guideline recommends the following:

- Testing ER and PgR status on all newly diagnosed invasive breast cancers (primary site and/or metastatic site), and whenever appropriate, repeat testing in patients with a known breast cancer diagnosis who now present with a local or distant recurrence.
- Establishing uniform testing measures that focus on proven, reliable and reproducible assays and procedures.
- Having testing laboratories validate their assays against existing and clinically validated tests. Results should agree at least 90 percent of the time with those of the clinically validated assays for positive receptor status and at least 95 percent for negative receptor status.
- Transporting breast tissue specimens from the operating room to the pathology laboratory as soon as they are available for gross assessment. The time from tumor removal to initiation of fixation should be kept to one hour or less. Fixation of the sample in neutral buffered formalin must extend for at least 6 hours and no longer than 72 hours.”

**April 19, 2010**

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“- Performing ER and PgR testing in a CAP-accredited laboratory or in a laboratory that meets the accreditation requirements spelled out in the guideline. The CAP will require that every accredited lab performing testing participate in a mandatory proficiency testing program.

- Considering an ER and PgR test performed by an IHC assay as positive if at least one percent of the tumor in the sample tests positive, which helps predict whether a patient is likely to benefit with endocrine treatment. The panel recognized that it is reasonable for oncologists to discuss the pros and cons of endocrine therapy with patients whose tumors contain low levels of ER by IHC (one percent to ten percent weakly positive cells) and to make an informed decision based on available information.”

April 20, 2010

# Cancer Fight: Unclear Tests for New Drug

By GINA KOLATA

QUOTATION OF THE DAY, April 20 2010

*“This is an issue that transcends breast cancer. A poorly developed test is potentially as dangerous as a poorly developed drug.”*

DR. ANTONIO WOLFF, of Johns Hopkins University, on unreliable results for a test linked to a groundbreaking therapy.

*“... a new drug [trastuzumab] misused could become “a toxic and expensive placebo.”*

April 29, 2010

LETTER

# Breast Cancer Tests

To the Editor:

Re "[Cancer Fight: Unclear Tests for New Drug](#)" (front page, April 20):

We appreciate your attention to the important issue of testing for breast cancer markers. Breast cancer is the most common cause of cancer death among women worldwide, including in low- and middle-income countries.

Fortunately, breast cancer mortality in the Western world has dropped dramatically over the last 30 years, in part because of widespread application of chemotherapy and, importantly, therapies that target estrogen and, more recently, HER2. But those therapies are only as good as the tests used to detect these markers.

**April 29, 2010**

The new guidelines issued by our organizations aim to increase the accuracy of testing by standardizing processes like tumor sample transfer to the pathology lab; improving performance and interpretation of the appropriate assays; and instituting rigorous and frequent proficiency testing to maintain laboratory accreditation.

Patients should also urge their oncologists and pathologists to insist that their breast cancer tests meet these new standards and are conducted in an accredited laboratory. Our organizations' patient Web sites — Cancer.Net and MyBiopsy.org — provide additional helpful guidance. Access to accurate testing for cancer tumor markers around the world is essential to ensure that we get the right lifesaving treatments to the right patients.

M. Elizabeth H. Hammond, Daniel F. Hayes, Antonio C. Wolff.  
Baltimore, April 21, 2010