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Breast Cancer

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Module 5 Introduction, by Dr. Vern Carruthers, PhD

- Module 5—breast and prostate cancer
  - Most prominent human cancers
  - Led by Drs. Nancy Davidson and Terry Brown

Breast Cancer: U.S. Statistics 2005

- 213,000 new cases
- 40,000 deaths
- Lead cancer diagnosis in women
- Second leading cause of cancer death in women

Potential Applications for Breast Cancer: Biology

- Predict risk of cancer development
- Estimate prognosis for established cancer
- Predict response to therapy
- Identify therapeutic targets

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Section A

Risk of Cancer

Breast Cancer Risk Factors: Demographics

- Gender
  - Male: female
    - 1:100
- Age
  - 1 in 50 by age 50
  - 1 in 8 over lifetime

Breast Cancer Risk Factors: Reproductive

- Early menarche
- Late menopause
- Nulliparity or late first pregnancy
- ? Lactation

Breast Cancer Risk Factors: Environmental

- Radiation—yes
- Pesticides—no
- Electromagnetic fields—no

Breast Cancer Risk Factors: Lifestyle

- Diet
- Alcohol
- Physical activity
- Tobacco

Breast Cancer Risk Factors: Endogenous Hormones

- ? High hormone levels
- Post menopausal obesity
- Increased bone density

Breast Cancer Risk Factors: Exogenous Hormones

- Hormone replacement therapy—yes
- Estrogen replacement therapy—no?
- Oral contraceptives—no

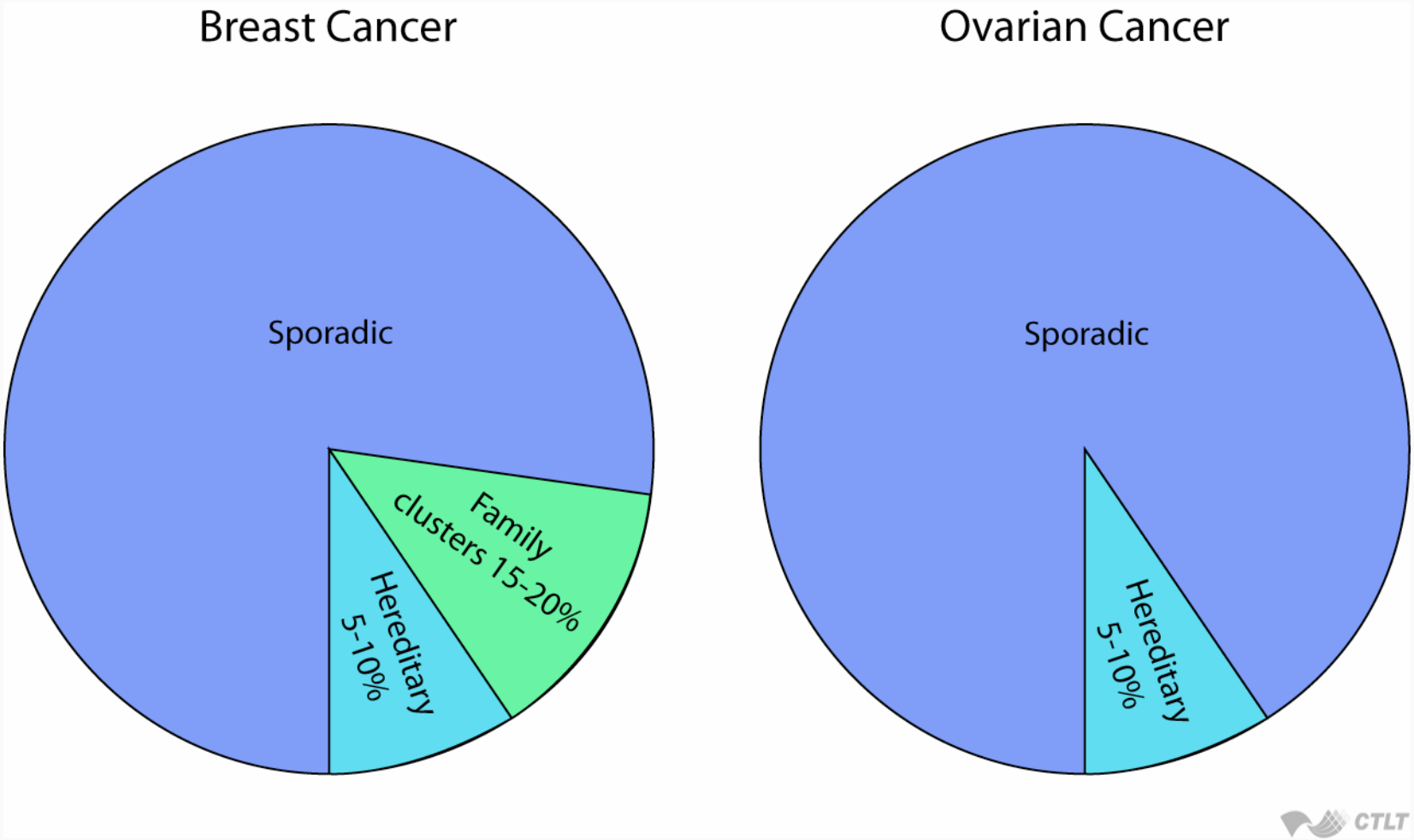
Breast Cancer Risk Factors: Pathology

- Atypical ductal or lobular hyperplasia
- Lobular carcinoma in situ

Breast Cancer Risk Factors: Inherited Susceptibility

- Family history
- Major inherited susceptibility
- DNA repair defects

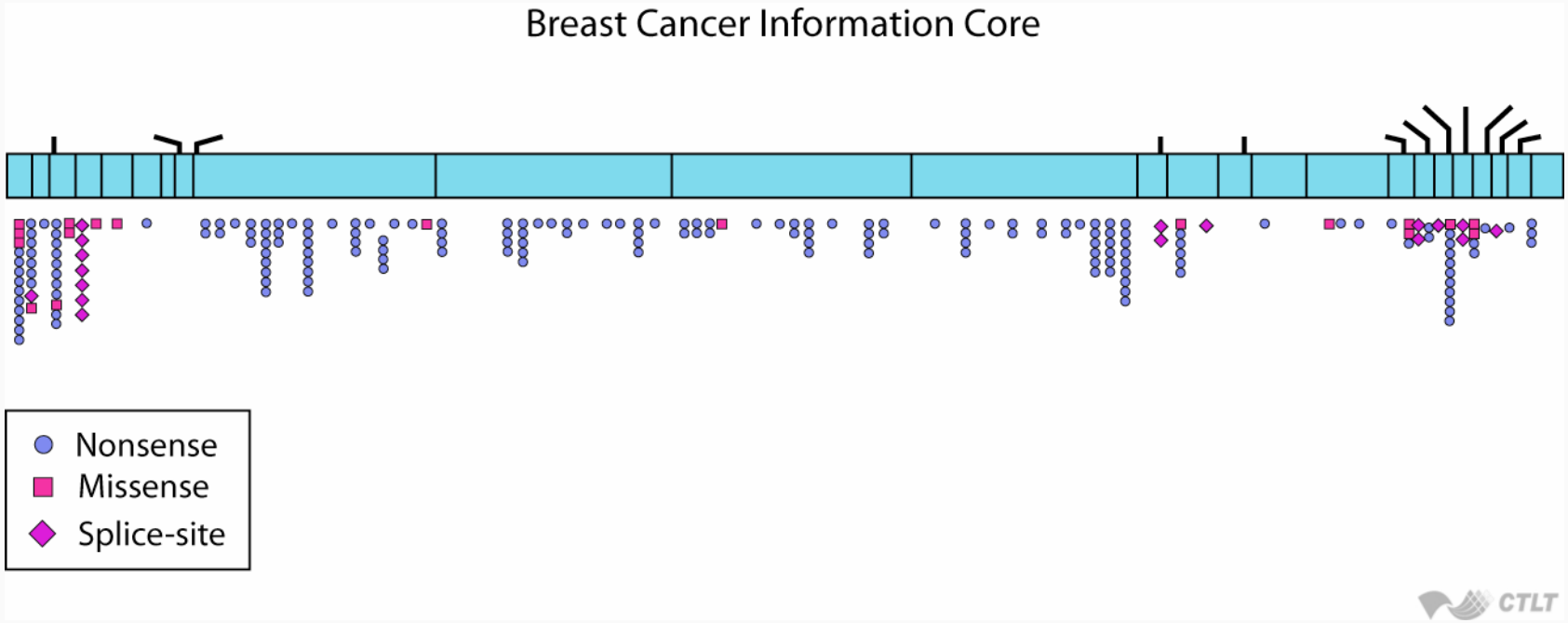
How Much Breast and Ovarian Cancer Is Hereditary?



Causes of Hereditary Susceptibility to Breast Cancer

Gene	Contribution to Hereditary Breast Cancer
BRCA1	20–40%
BRCA2	10–30%
TP53	<1%
PTEN	<1%
Undiscovered genes	30–70%

- Tumor suppressor gene on chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~500 different mutations reported

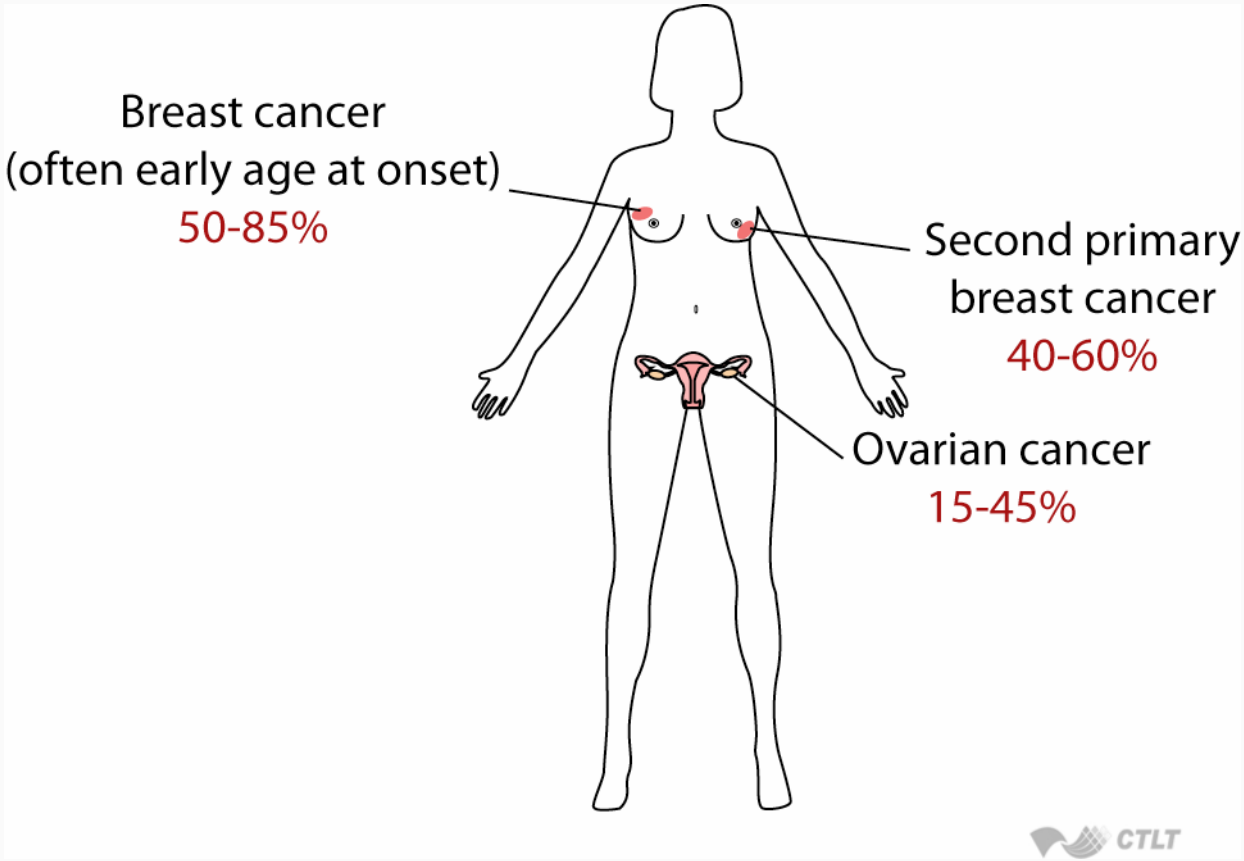


Increased Likelihood of BRCA Mutations

- Features that indicate increased likelihood of having BRCA mutations
  - Multiple cases of early onset breast cancer
  - Ovarian cancer (with family history of breast or ovarian cancer)
  - Breast and ovarian cancer in the same woman
  - Bilateral breast cancer
  - Ashkenazi Jewish heritage
  - Male breast cancer

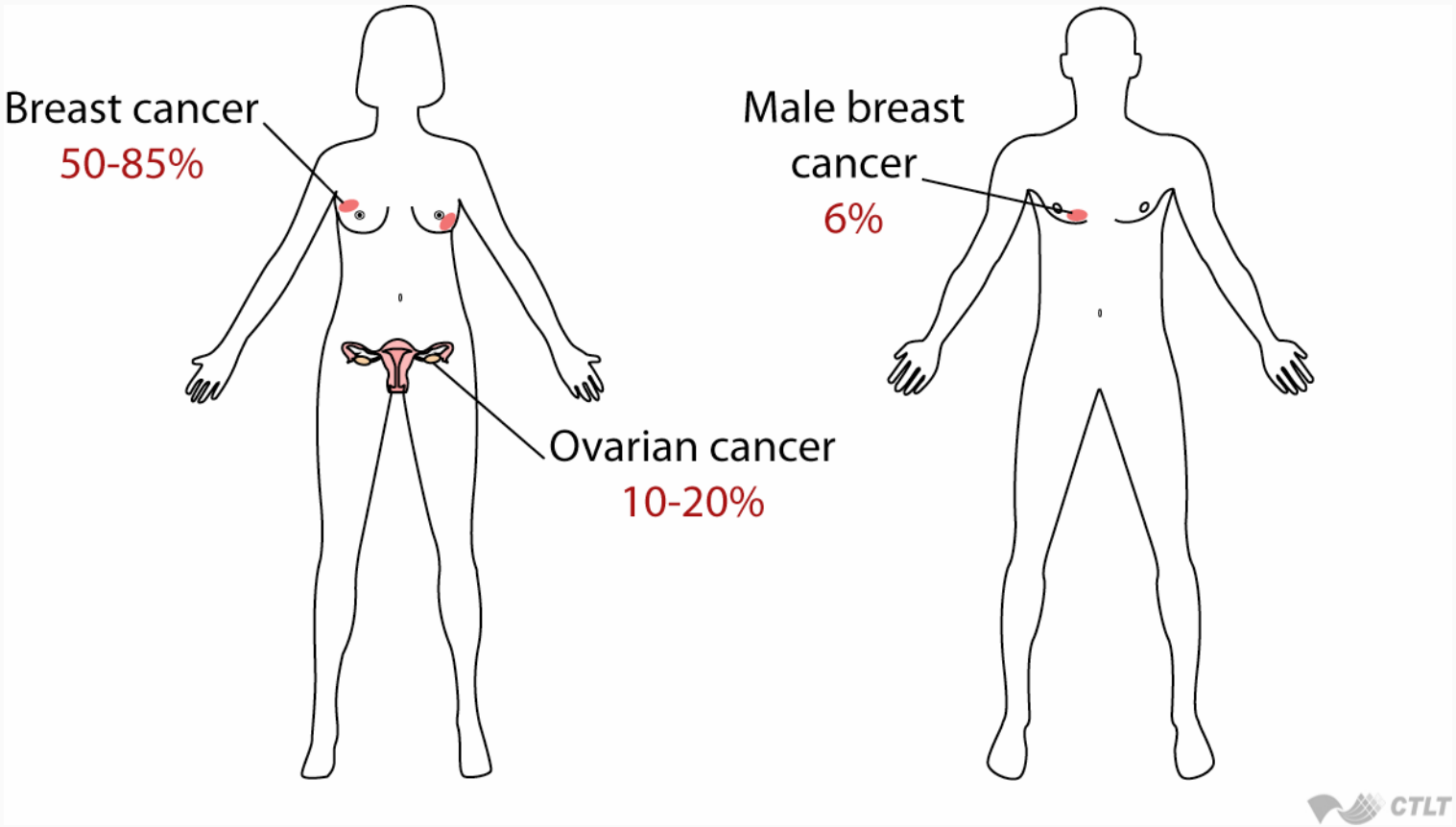
BRCA1-Associated Cancers: Lifetime Risk

- Possible increased risk of other cancers (e.g., prostate, colon)

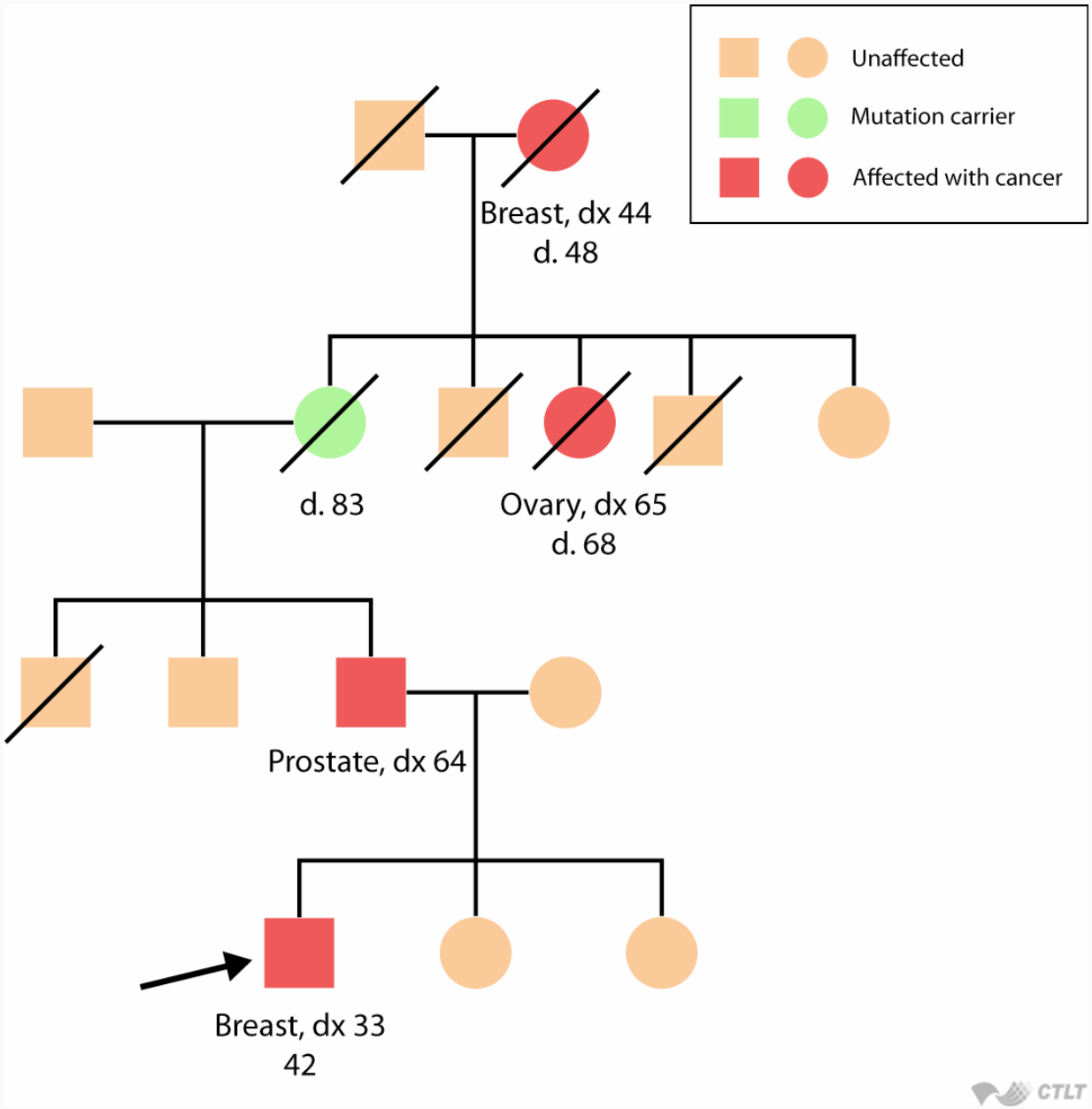


BRCA2-Associated Cancers: Lifetime Risk

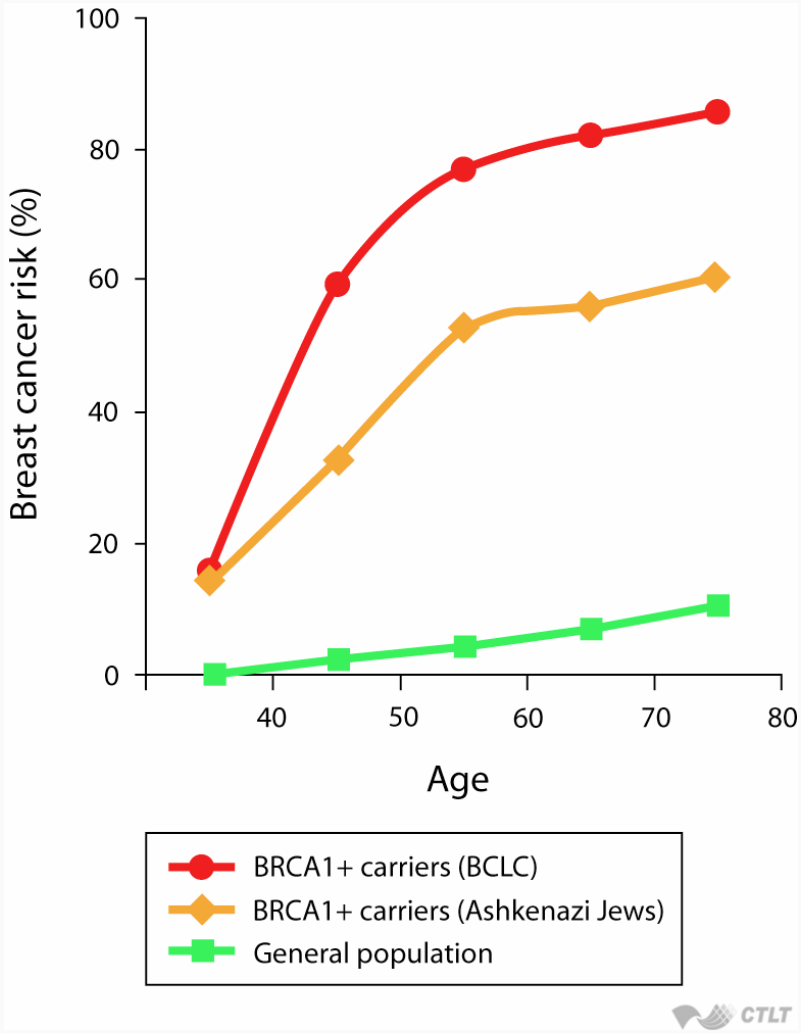
- Increased risk of prostate, laryngeal, and pancreatic cancers (magnitude unknown)



BRCA2-Linked Hereditary Breast Cancer



Breast Cancer Risk Estimates in BRCA Mutation Carriers



Adapted by CTLT from: Source*:* Adapted by *Easton, D.F., Ford, D., Bishop, D.T. (1995).* Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Hum *Genet; 56:265–71. Struewing, J.P., Hartge, P., Wacholder, S. (1997), et al.* The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med*; 336:1401–8.*
ASCO.org. See ASCO Curriculum

Options for Carriers of BRCA-1 or BRCA-2 Mutations

- Surveillance
- Chemoprevention
- Prophylactic surgery

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Section B

Prognosis for Established Cancer and Response to Therapy

Prognostic Markers for Breast Cancer

- Established at the NIH Consensus Conference 2003
  - Axillary lymph nodes
  - Tumor size
  - Histological grade
  - Histological tumor type
  - Steroid receptor states
  - Age

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Potential Applications for Breast Cancer Biology

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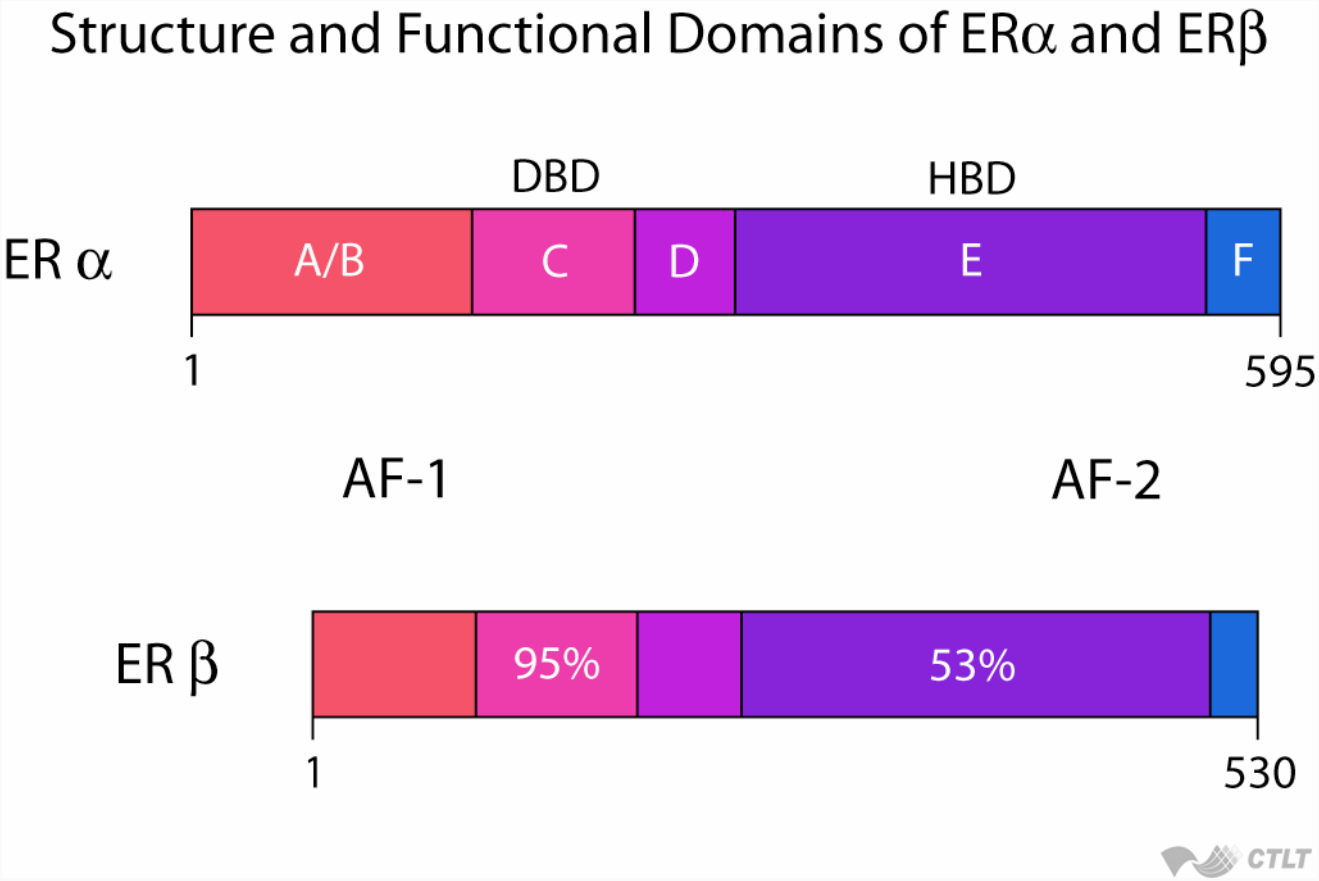
The Estrogen Receptors



Source: Adapted by Osborne, C.K., Zhao, H., Fuqua, S.A. (2000).
Selective estrogen receptor modulators: structure, function, and clinical use. J Clin Oncol*; 18:3172–86.*

Steroid Receptors in Breast Cancer

Steroid Receptors in Breast Cancer		
Tumor phenotype	Phenotype frequency	Response to hormonal therapy
ER+/PR+	41%	75–80%
ER+/PR-	30%	20–30%
ER-/PR+	2%	40–45%
ER-/PR-	27%	<10%

Source: McGuire (1978)

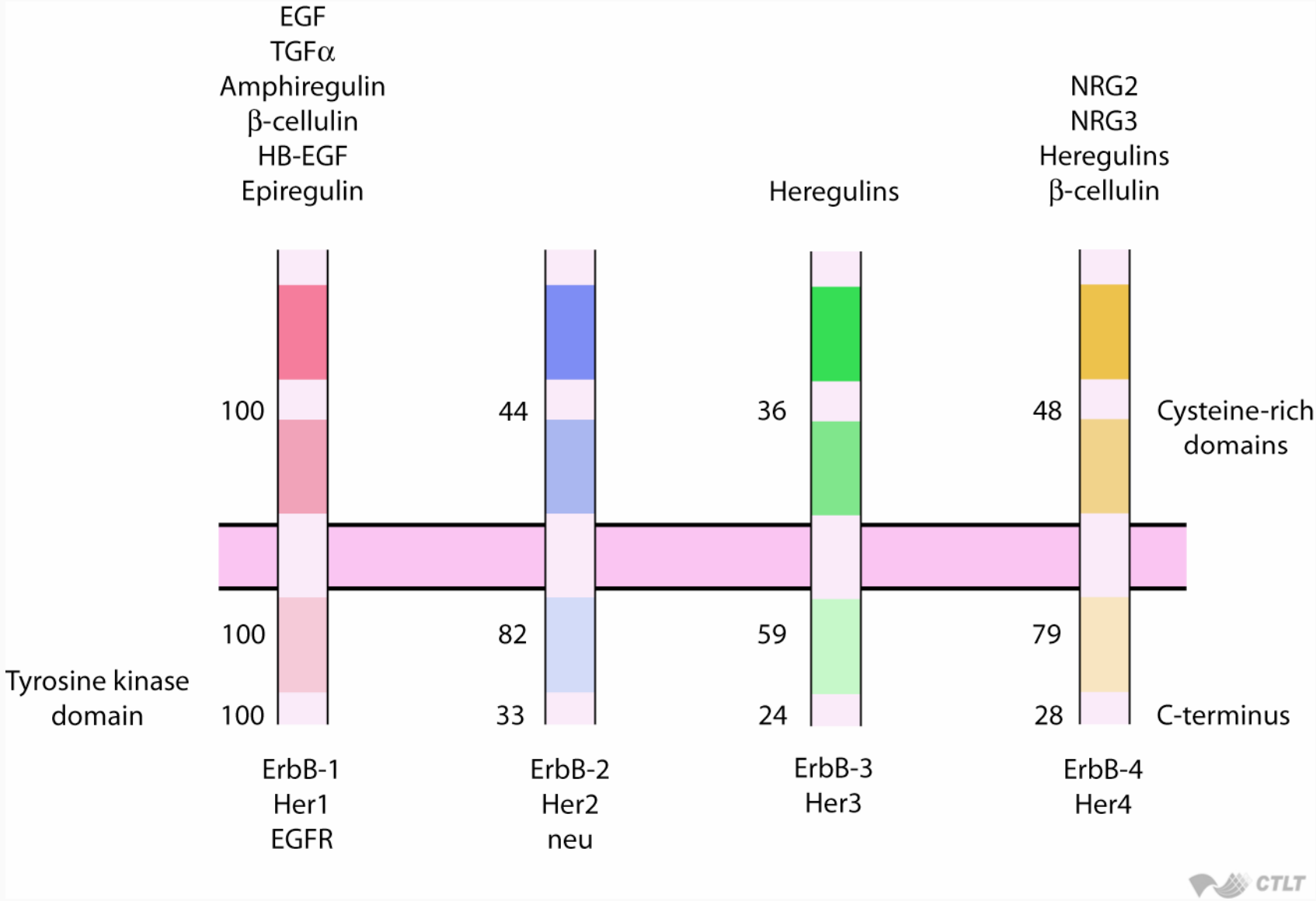
Endocrine Therapy for Breast Cancer

- Ovarian ablation—surgery, radiation, LHRH agonists
- SERMs—tamoxifen, toremifene, fulvestrant
- Aromatase inhibitors—anastrozole, letrozole, exemestane
- Additive—progestins, estrogens, androgens

Some Possible Mechanisms of Hormone Resistance

- Loss of ER expression
  - Mutation or deletion
  - Promoter methylation
  - Altered transcriptional factors
- Altered coactivators or corepressors
- Alternative growth factor pathways
- Drug delivery

The EGFR (ErbB) Family and Ligands



HER 2 As a Predictive Marker for Trastuzumab

HER 2 as a Predictive Marker for Trastuzumab	
HER 2 Status	Response Rate
IHC 3+	35%
IHC 2+	0
FISH positive	34%
FISH negative	7%

Source: Vogel (2002), JCO

HER 2 as a Predictive Marker

- ? Resistance to tamoxifen
- ? Response to anthracycline

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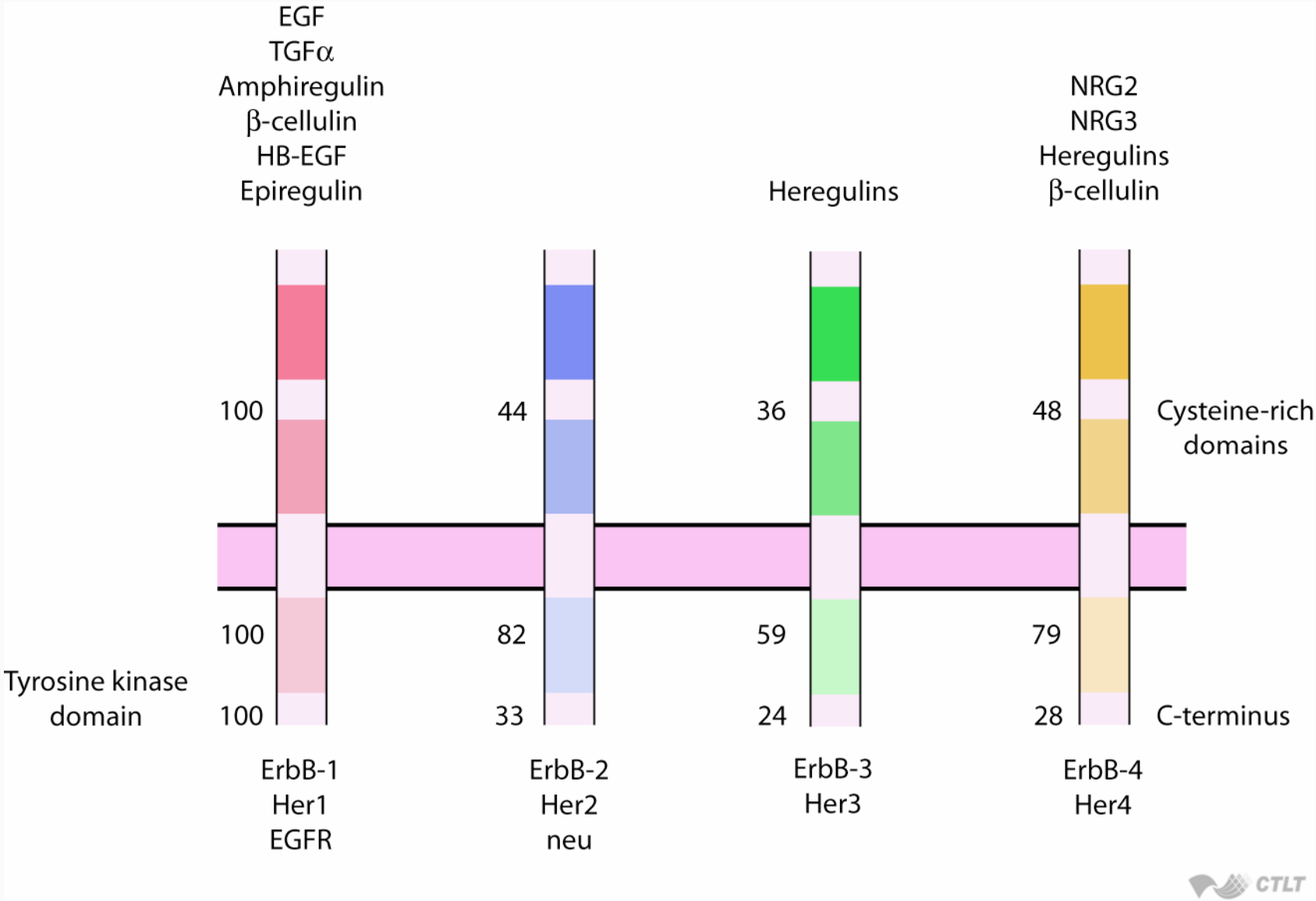
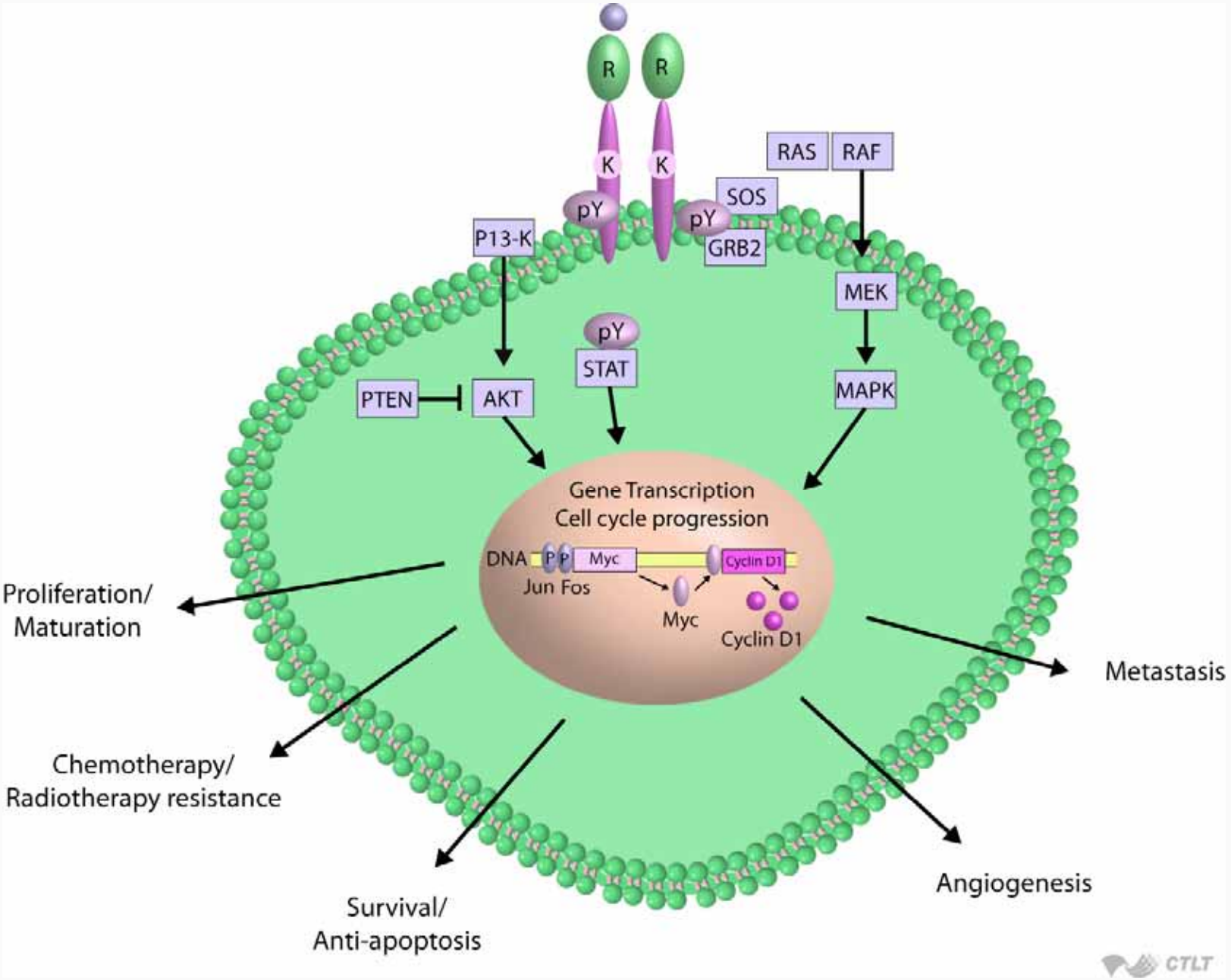
Section C

New Therapeutic Targets for Breast Cancer

The EGFR (ErbB) Family and Ligands



EGFR Signal Transduction in Tumor Cells



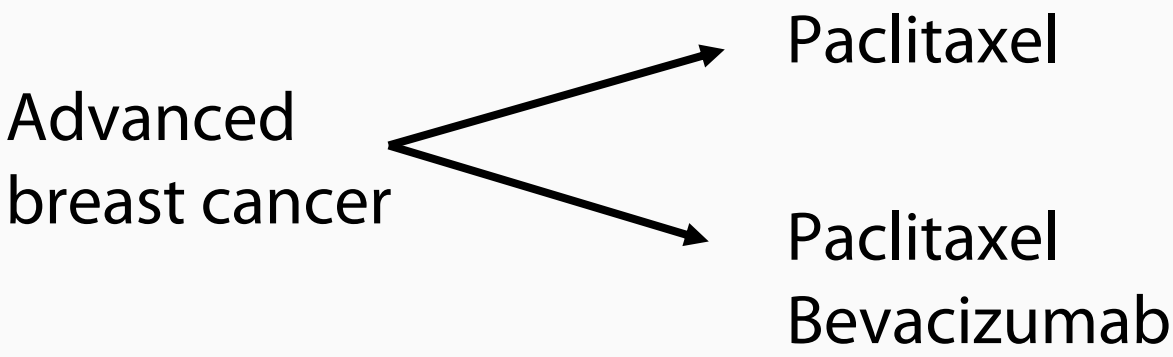
Available Forms of Anti-EGFR Therapy

- Antibody-based
  - Cetuximab
- Small molecule TKI
  - Gefitinib
  - OSI774

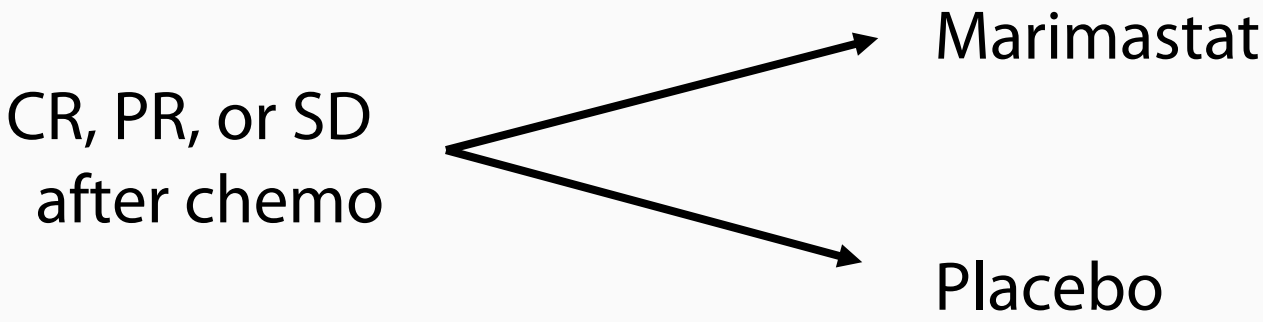
Therapy Against Other Targets

- Anti-angiogenic
  - anti–VEGF
    - bevacizumab
- Matrix metalloproteinase inhibitors
- Bisphosphonates

- Twenty percent clinical benefit in advanced breast cancer



- No effect on time to progression



Application of Arrays

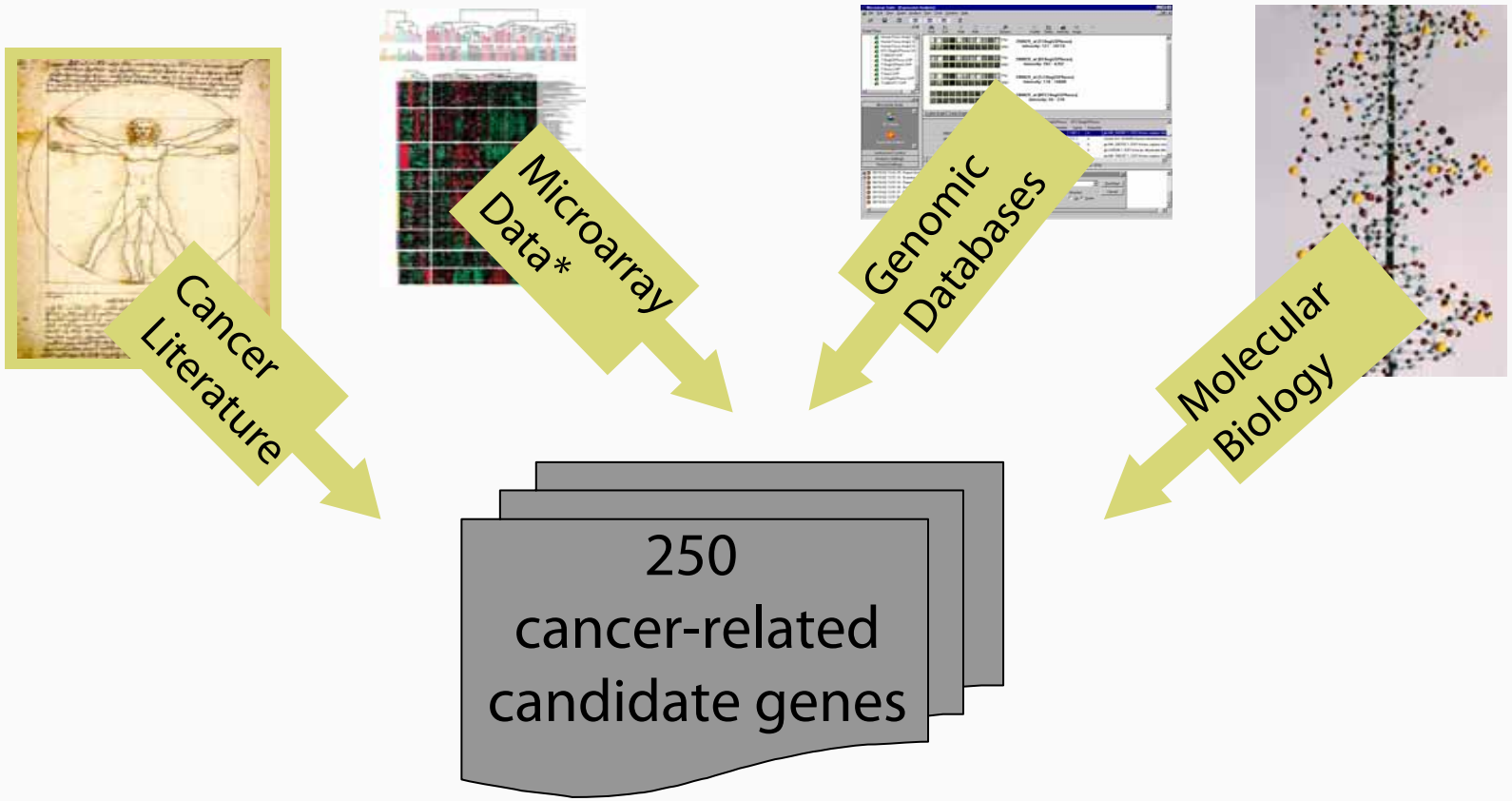
- Different profile of sporadic versus hereditary breast cancer
  - Heldenfalk et al. (2001), NEJM
- Identify subset of young women with poor prognosis early breast cancer
  - van't Veer et al. (2002), Nature
- Lack of profile for response to doxorubicin
  - Perou et al. (2000), Nature

Oncotype DX Breast Cancer Assay

- Now available—$3400
- Should we use it?
- For whom?
- How?

Candidate Gene Selection

- Candidate gene selection from ~40,000 genes



Example Papers: Van 't Veer et al. (2002). Nature; 415:530; Sorlie, et al. (2001). Proc. Natl. Acad. Sci. U.S.A.; 98:10869; Ramaswamy, et al. (2003). Nature Genetics; 33:4; Gruvberger et al. (2001). Cancer Res; 61:5979

Three Breast Cancer Studies Used to Select

Sixteen Cancer and Five Reference Genes

PROLIFERATION	INVASION	HER2	ESTROGEN	REFERENCE
Ki-67 STK15 Survivin Cyclin B1 MYBL2	Stromelysin 3 Cathepsin L2 Best RT-PCR performance and most robust predictors	GRB7 HER2 GSTM1 CD68 BAG1	ER PGR Bcl2 SCUBE2	Beta-actin GAPDH RPLPO GUS TFRC

CTLT

Source: Adapted by CTLT from Paik et al. (Dec. 30, 2004) N Engl J Med.

Three Studies Develop Recurrence Score (RS) Algorithm

Three Breast Cancer Studies Used to Develop Recurrence Score (RS) Algorithm	
RS =	+0.47 x HER2 Group Score
	-0.34 x ER Group Score
	+1.04 x Proliferation Group Score
	+0.10 x Invasion Group Score
	+0.05 x CD68
	-0.08 x GSTM1
	-0.07 x BAG1

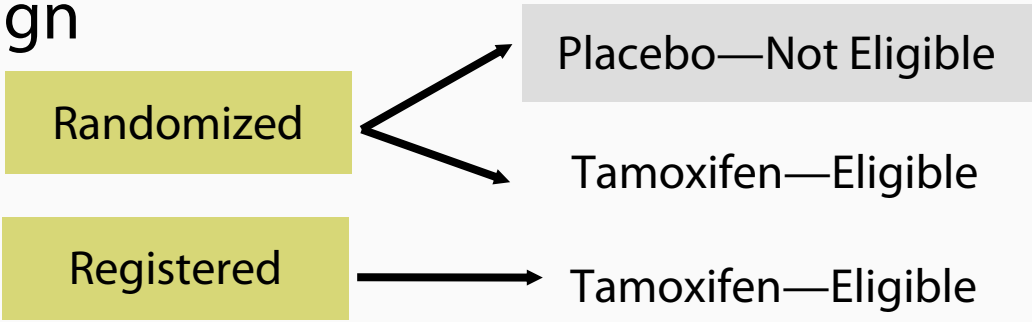
Continued

Three Studies Develop Recurrence Score (RS) Algorithm

Recurrence Category	RS (0–100)
Low risk	<18
Intermediate risk	18–30
High risk	• 31

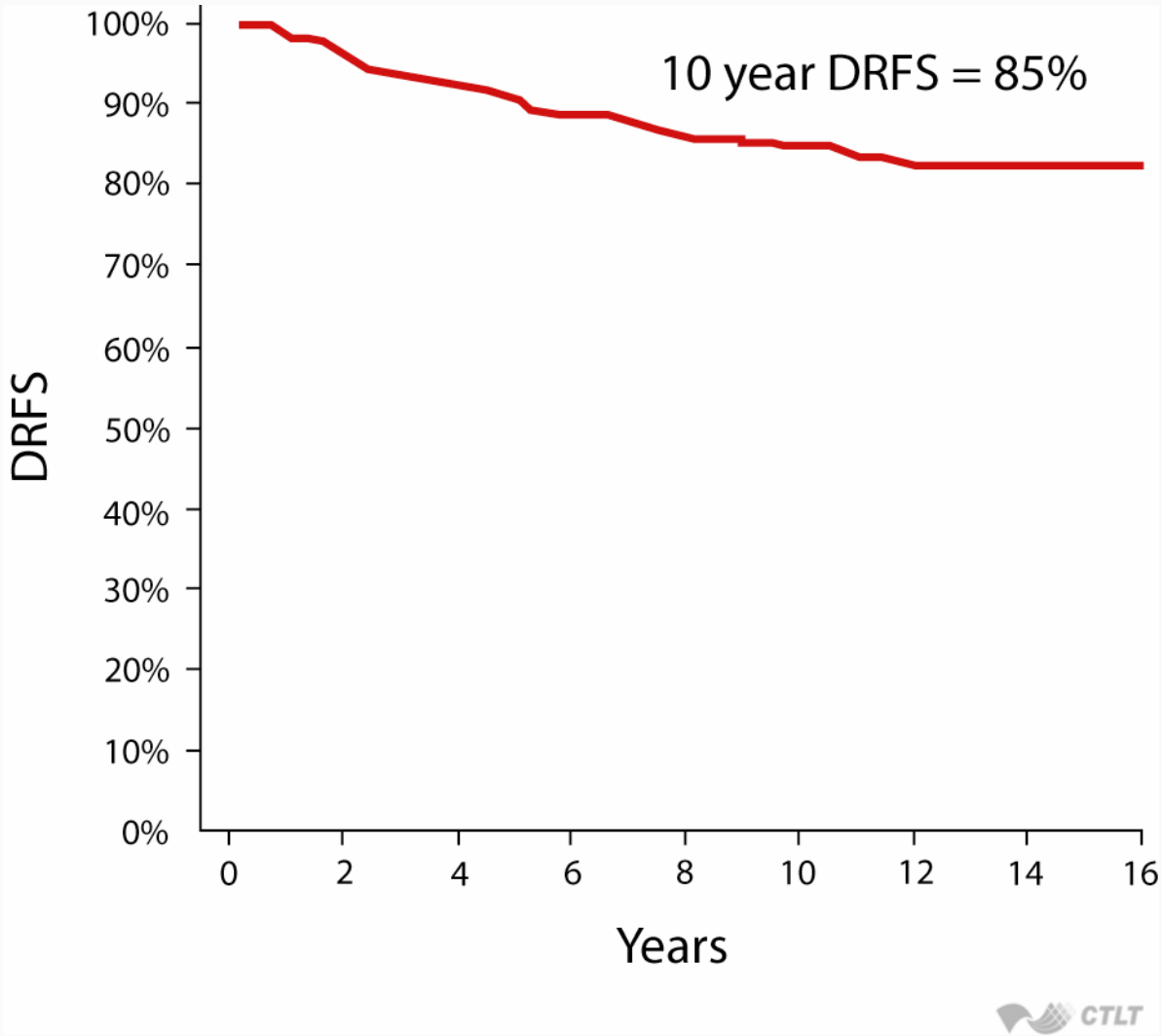
Prospective Clinical Validation Study

- Objective
  - Validate Recurrence Score as predictor of distant recurrence in N-, ER+, tamoxifen-treated patients
- Design



  - Pre-specified 21 gene assay, algorithm, endpoints, analysis plan
  - Blinded laboratory analysis of three 10 µ sections

- DRFS—All 668 Patients



Source: Adapted by CTLT from Paik et al. (Dec. 30, 2004), N Engl J Med.

- B-14 Results
  - First Primary Objective
    - Validate that 10 year DRFS in the low-risk group (RS < 18) is significantly higher than 10 year DRFS in the high risk group (RS ≥ 31)
    - Assuming: binomial test for differences in proportions = 0; $\alpha = 0.05$; 600 evaluable patients—240 low-risk patients with DRFS 0.90 and 150 high-risk patients with DRFS 0.70; then power >95%

Source: Adapted by CTLT from Paik et al. (Dec. 30, 2004), N Engl J Med.

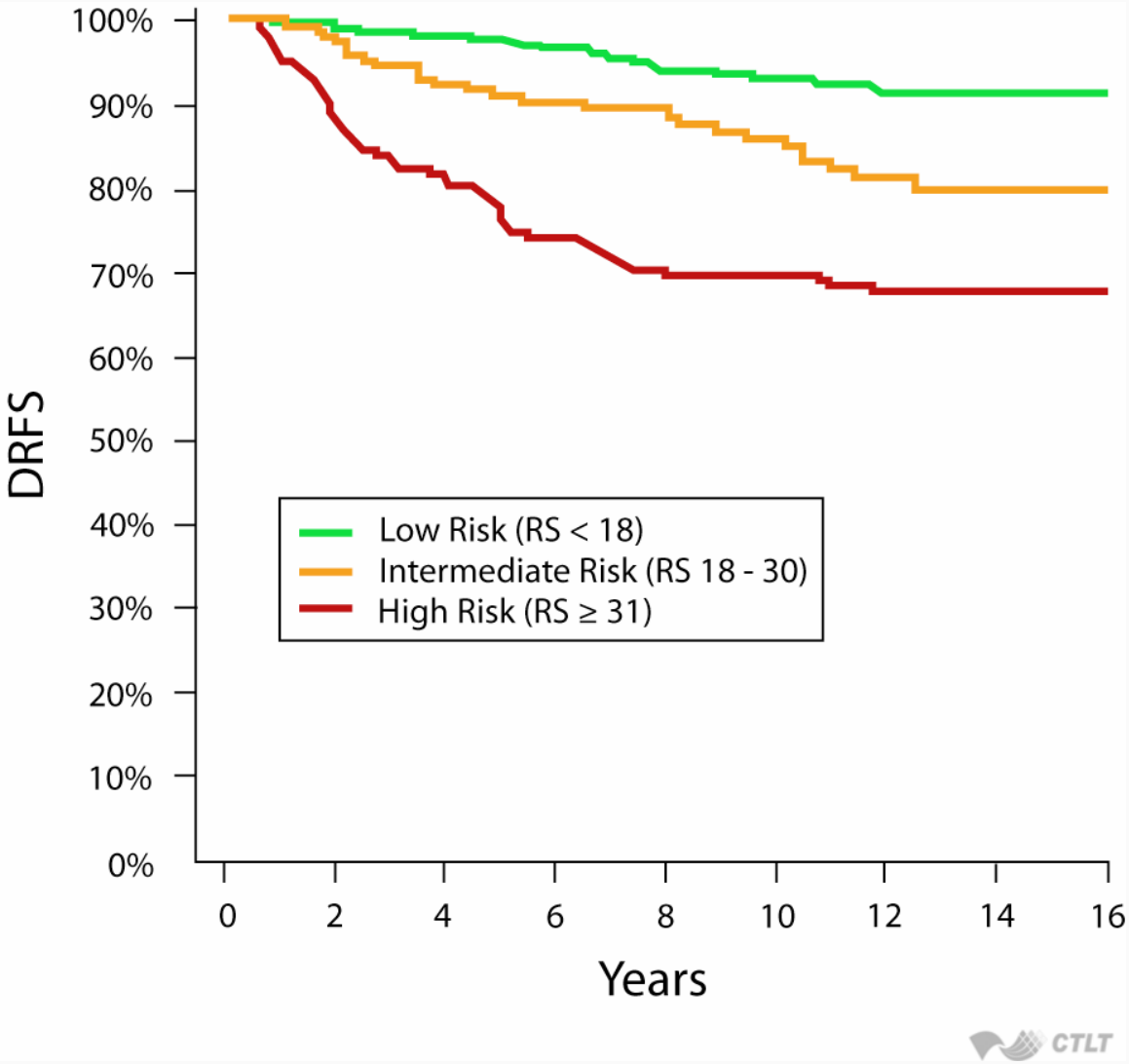
DRFS—Low-, Intermediate-, and High-RS Groups			
Risk Group	**Percentage of Patients**	**10-year Rate Recurrence**	**95% CI**
Low (RS < 18)	51%	6.8%	4.0%, 9.6%
Intermediate (RS 18–30)	22%	14.3%	8.3%, 20.3%
High (RS • 31)	27%	30.5%	23.6%, 37.4%

Test for the 10-year DRFS comparison between the low- and high-risk groups: p<0.0001

Source: Adapted by CTLT from Paik et al. (Dec. 30, 2004), N Engl J Med.

Continued

- DRFS—Low-, Intermediate-, High-RS Groups



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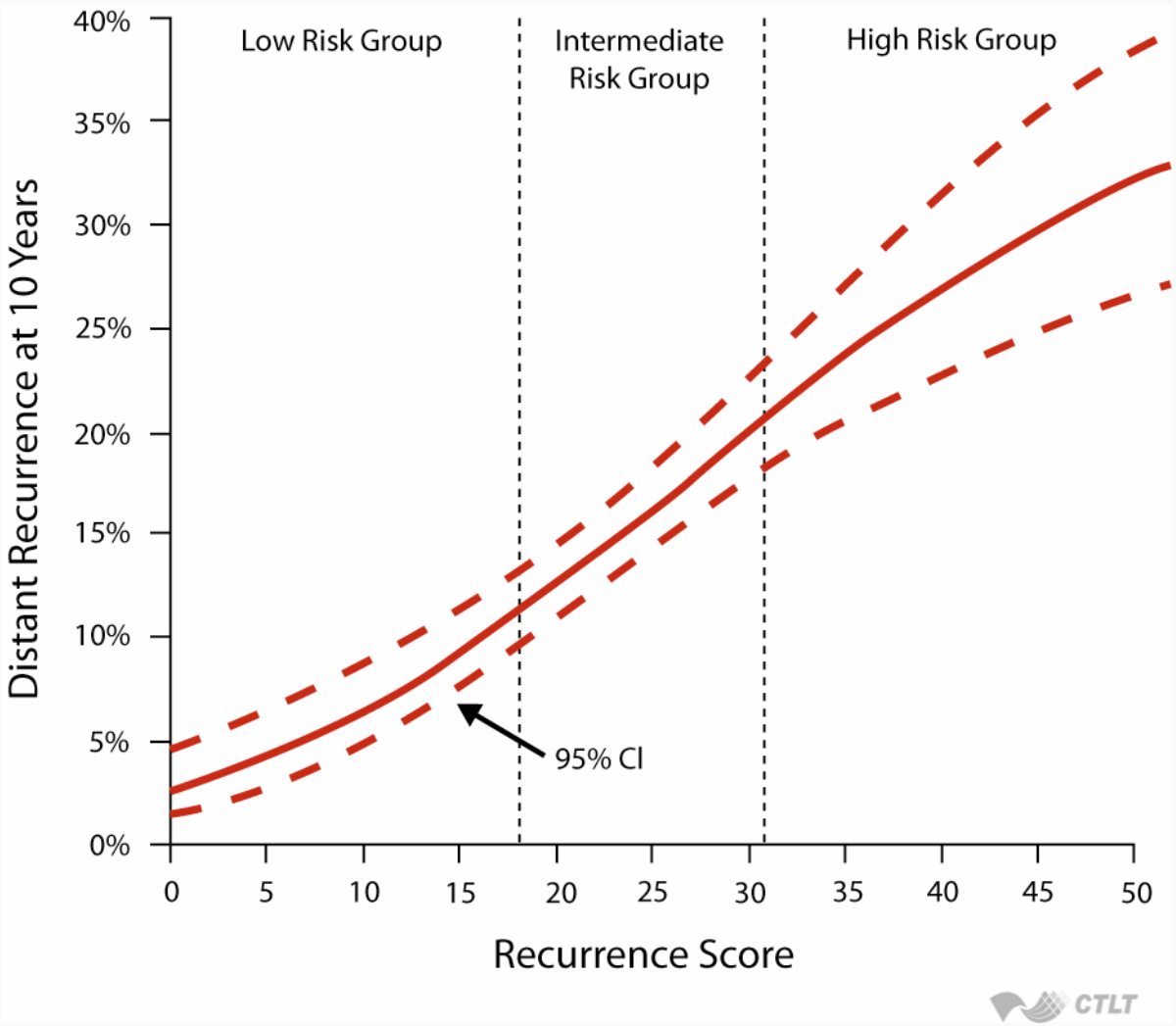
Recurrence Score As a Continuous Predictor



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Potential Applications for Breast Cancer Biology

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