Introduzione e place in therapy best paper

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Disclosure slide

Advisory/consultancy role/speaker bureau:

- Eli Lilly
- Pfizer
- Novartis
- Roche
- AstraZeneca
- MSD
- Daiichi Sankyo
- Gilead
- Seagen

Impact of Aromatase SNPs in ER+/HER2- Breast Cancer: Towards Personalized Therapy

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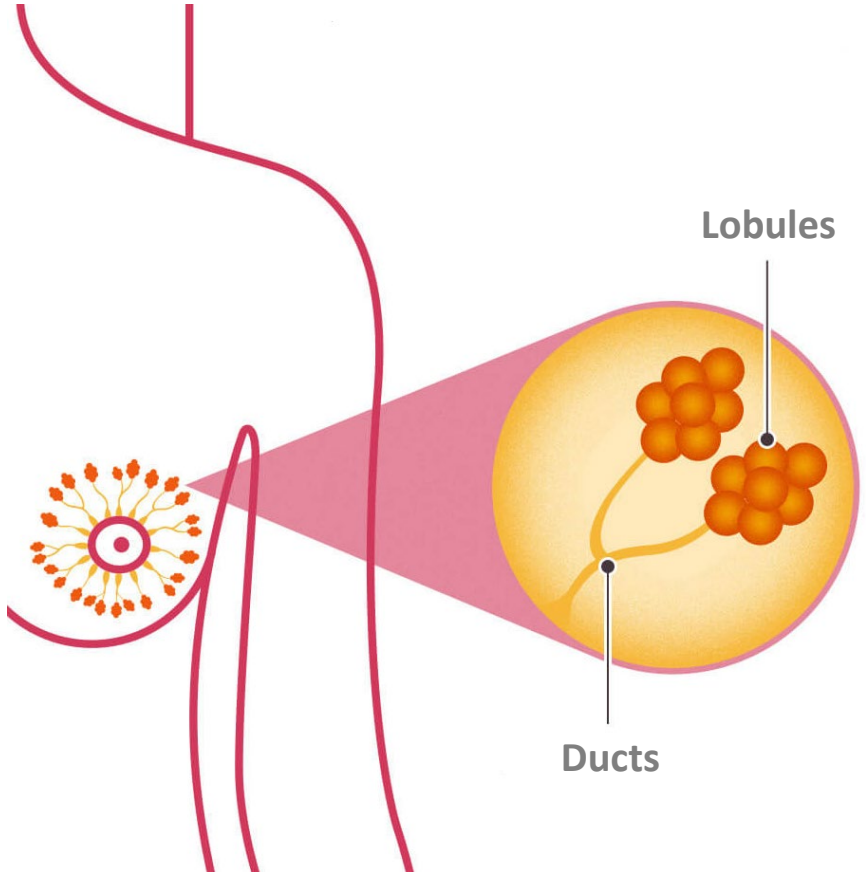
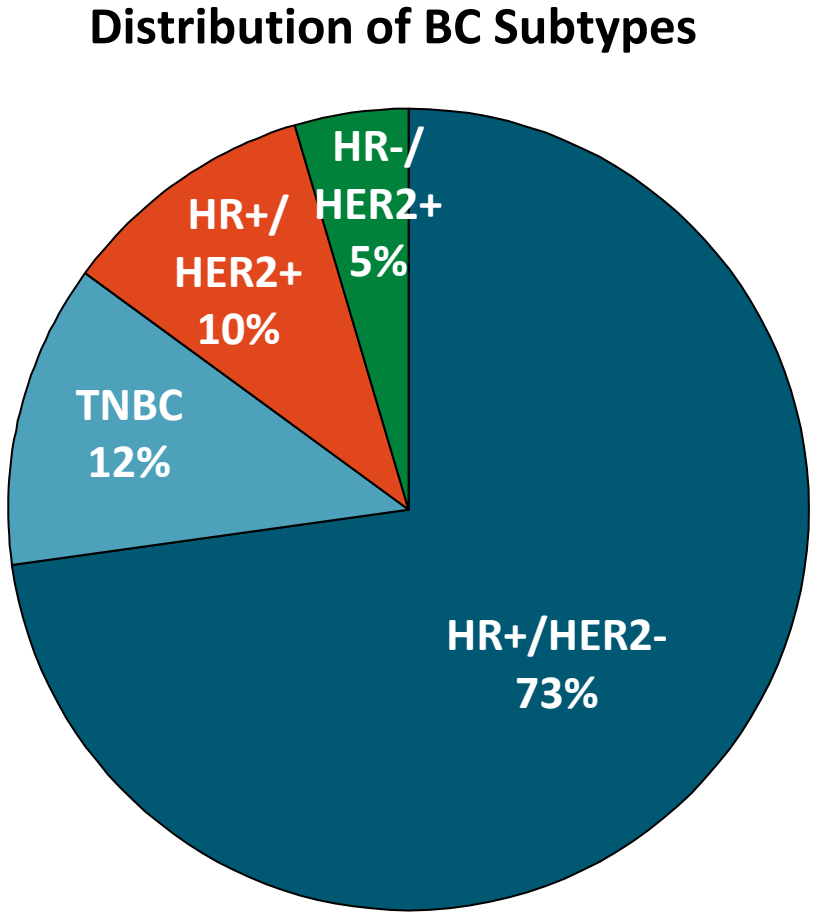
HR+/HER2- Breast Cancer

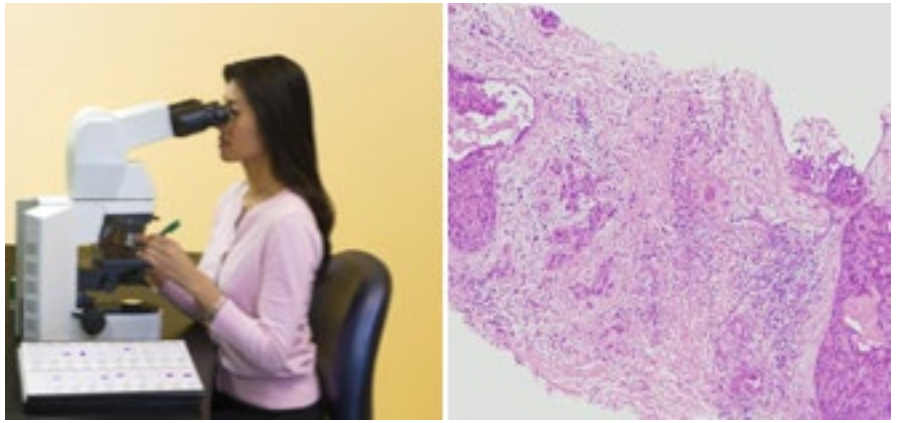




NIH SEER. Cancer stat facts: female breast cancer; Howlader N, et al. J Natl Cancer Inst. 2014; Brufsky AM. Cancer Treat Rev. 2017

Parameters Used to Inform Treatment Decisions

- Tumour size
- Lymph node status
- Grade
- Patient age
- ER / PR, HER2, Ki-67
- Genomic tests



Luminal BC therapy has become more diverse

- Endocrine Therapy (ET)
- Escalated ET
- ET + Chemotherapy (CHT)
- Escalated ET + CHT
- ET + targeted agents

Which Adjuvant Endocrine Therapy?

Post-menopausal Patients

- Aromatase inhibitor for 5 years is better than tamoxifen for 5 years
- Sequencing Tamoxifen (2-3ys) and AI (2-3ys) is an alternative to 5 years of AI
- Tamoxifen for 5 years for select low-risk patients

Tamoxifen vs. AI monotherapy

Trial	Agents	Patient population	Median FU	DFS	Other comments	OS
ATAC	ANA vs. TAM (vs. both)	60% LN- 24% 1-3 LN+ 9% 4+ LN 64%T</=2cm	10 yrs	HR 0.85 for ANA, 95% CI 0.76–0.94	DFS findings NS for LN- pr T</=2cm	NS
BIG 1-98	LET vs. TAM	41% LN+ 62% T</=2cm	12.6 yrs	HR 0.91 for LET; 95% CI 0.81-1.01	DFS findings NS for T</=2cm or LN-	NS

AI monotherapy is superior to tamoxifen monotherapy with regard to DFS but not OS (and perhaps not in lowest risk patients)

Lancet Oncol 2002 and 2010, NEJM 2005, JCO 2019

Early Switch Strategies

Trial	Agents	Population	Median FU	DFS	Comments	OS
IES	TAM vs. TAM→EXE	50% N0 30% N1 14% N2	10 yrs	**HR 0.81** for EXE, 95% CI 0.72-0.92	N0 had improved DFS	NS (except ER+)
ARNO 95	TAM vs. TAM→ANA	74% N0 20% N1 6% N2 64% T1	≈ 6 yrs	**HR 0.66** for ANA, 95% CI 0.44-1.00	Combined w/ ABCSG 8 – similar findings	NS
ITA	TAM vs. TAM→ANA	45% T1 60s% N1 30s % N2-N3	5+ yrs	**HR 0.56** for ANA, 95% CI 0.35-0.89	All patients had positive nodes	NS
TEAM	EXE vs. TAM→EXE	53% N0 42% N1 5% N2-N3 58% T1	10 yrs	**No difference**	Similar to BIG 1-98	NS
BIG 1-98	TAM→LET LET→TAM (vs. LET)	58% N0 56% T1	12+ yrs	**No difference**	Similar to TEAM	NS

Switch strategies in the first 5 years are superior to tamoxifen alone and mirror AI monotherapy data, but OS is substantially not different across combinations.

Lancet Oncol 2017, NEJM 2004 and JCO 2017, NEJM 2009, Lancet Oncol 2011, JCO 2019, JCO 2016, JCO 2005 and Ann Oncol 2006

Treatment duration?

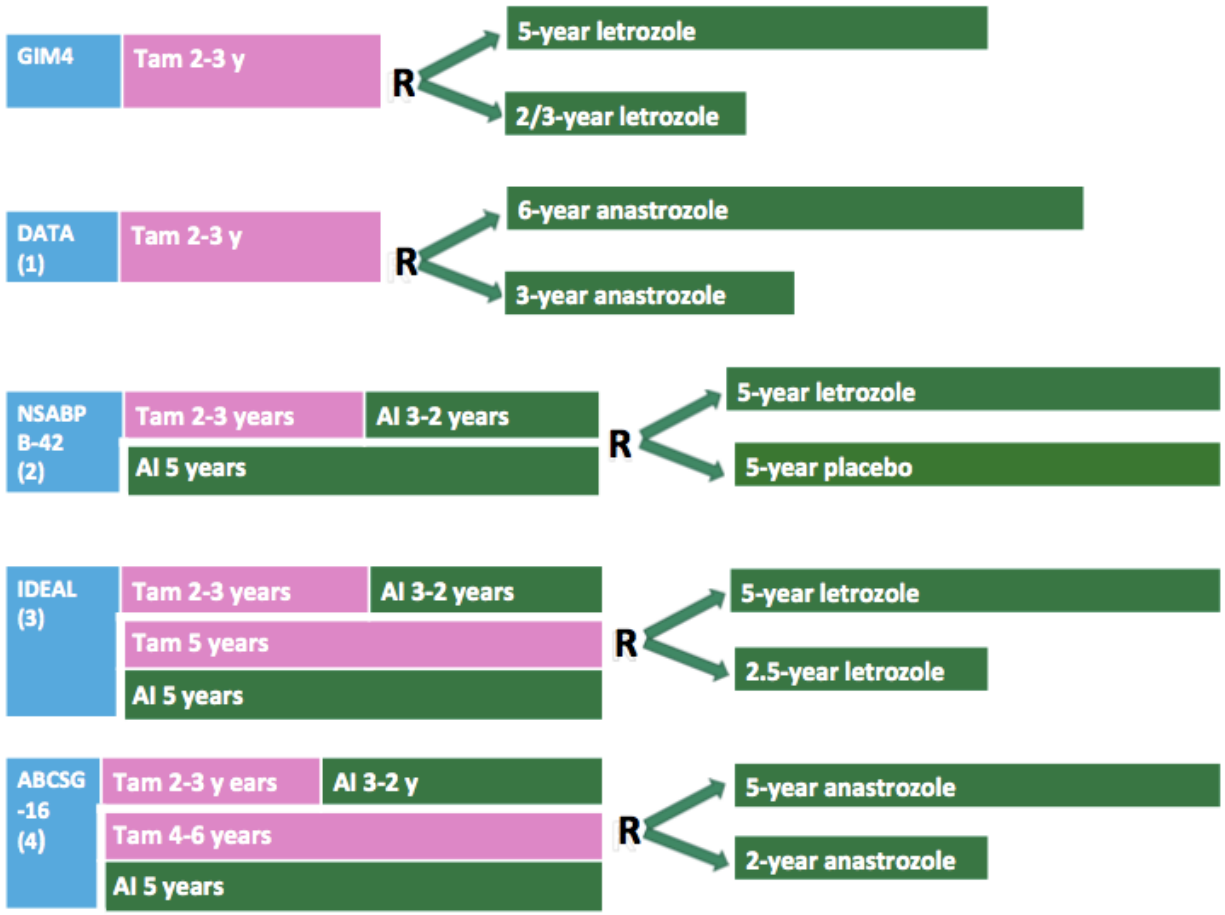
Post-menopausal Patients

- 5 vs 7/8 vs 10 years of treatment (?)

Long term risk of recurrence in HR+ BC

- The risk of relapse remains over time despite 5 years of ET
- More relapses occur after 5 years than in the first 5 years
- Risk of relapse remains constant to 20 years of follow-up (and presumably beyond)

Extended ET in postmenopausal patients



DFS Hazard ratio
0.78 (0.65-0.93)
0.79 (0.62-1.02)
0.84 (0.74-0.96)
1.007 (0.87-1.16)
0.92 (0.74-1.16)

- **7-8 years of adjuvant ET not inferior to 10 years**
- **7-8 years may represent a good compromise between efficacy and tolerability**
- **Still controversial whether upfront AIs is still the best option**

Balancing Benefits with Toxicity

Tamoxifen:

- More thromboembolic events
- Fewer bone fractures
- Fewer musculoskeletal events
- Less arthralgia
- Small added endometrial cancer risk
- No difference in survival when compared with AIs for most patients

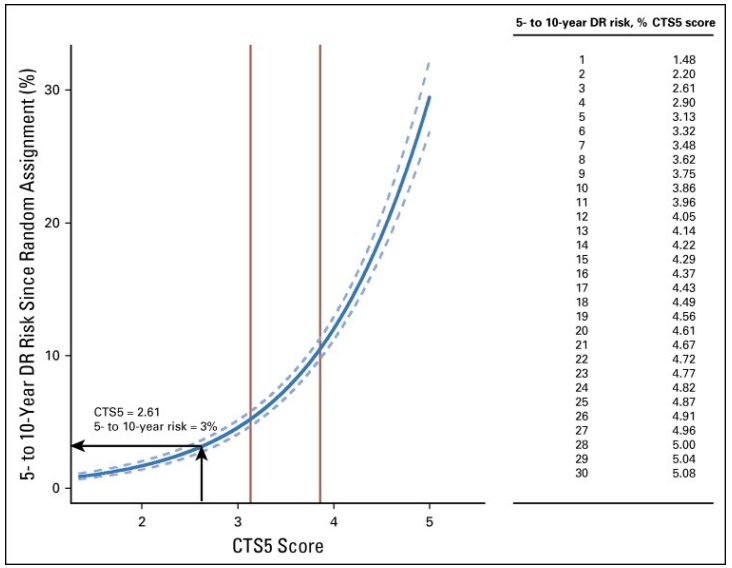
Similar: Cardiovascular events? QOL?
Longer time on ET = more events

Aromatase Inhibitor:

- More bone density loss and fractures
- More toxicity overall? (BIG 1-98)
- No added endometrial risk
- Fewer thromboembolic events
- Less cognitive impairment? (BIG 1-98)
- DFS advantage, perhaps more apparent in the setting of higher-risk disease

Risk scores to predict benefit of extended ET or alternative treatment strategies?

Signature
CTS5
IHC4
RS
BCI
ROR
EPclin



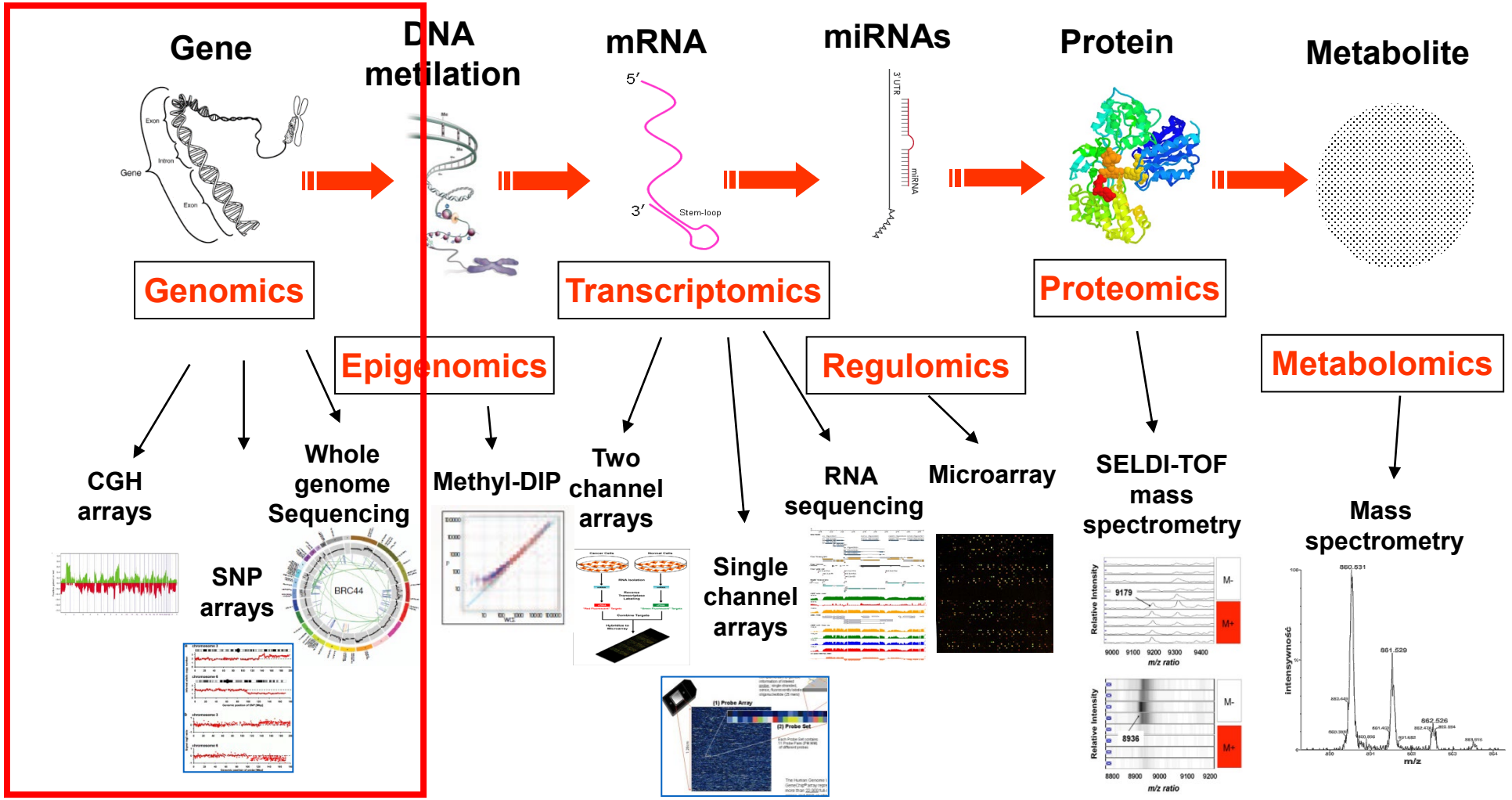
NCCN Guidelines Version 4.2023
Invasive Breast Cancer

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF EXTENDED ADJUVANT SYSTEMIC THERAPY[a,b]

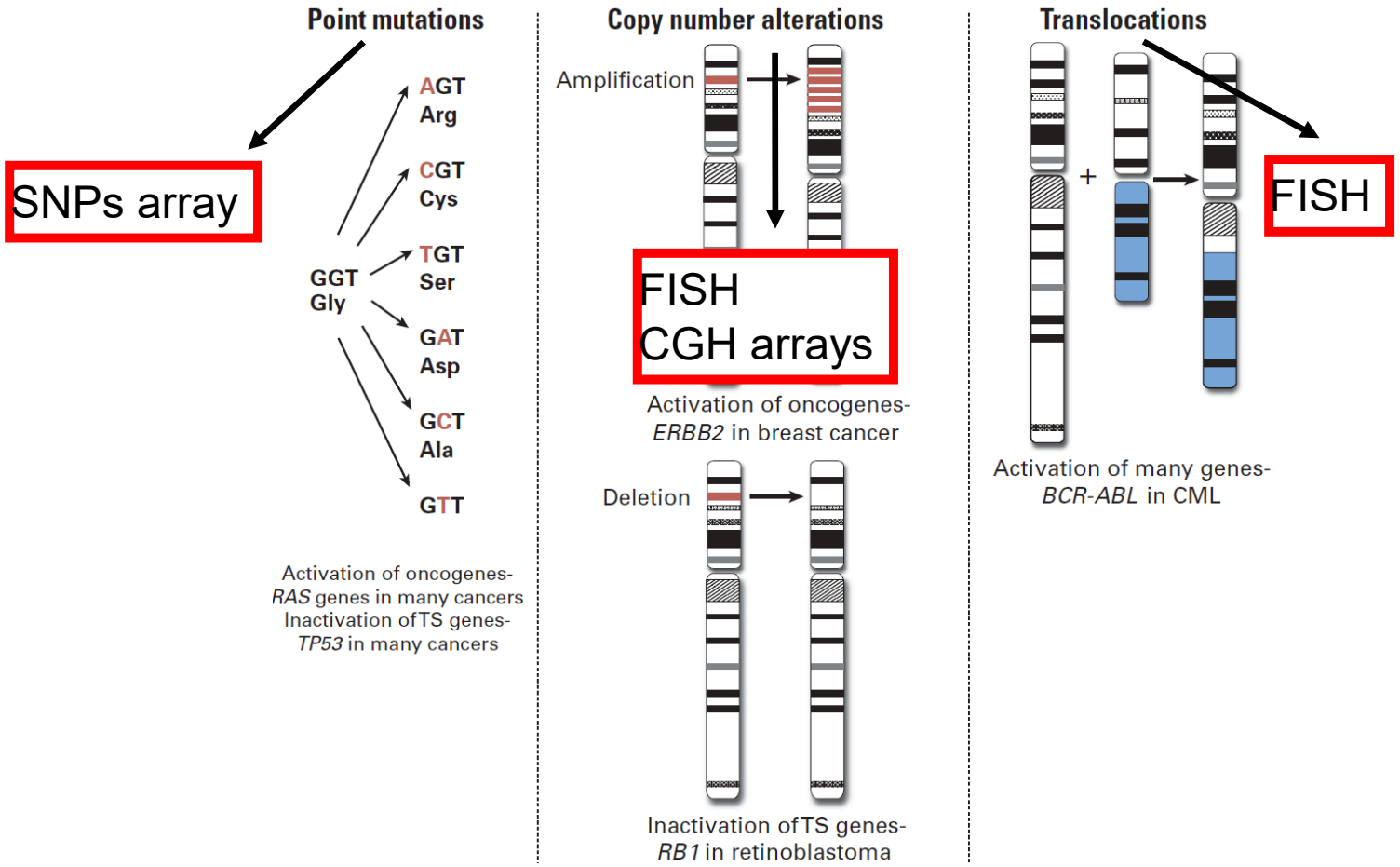
Assay	Recurrence Risk/ Predictive Result	Treatment Implications
Breast Cancer Index (BCI)	BCI (H/I) Low	• For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) in the low-risk range (0–5), regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0. • Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in disease-free survival (DFS) or OS compared to the control arm in terms of extending endocrine therapy duration.[8]
	BCI (H/I) High	• For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) high (5.1–10) demonstrated significant rates of late distant recurrence. • In secondary analyses of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1–T3, pN0 or pN+ who had a BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm.[8-11] • In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy.[8]

Dowsett M et al. *J Clin Onc.* 2018

The premise of precision medicine is to reveal the molecular landscape of cancer



The major classes of genomic alterations that give rise to cancer



MaccConaill LE & Garraway LA JCO 2010

SNPs in the era of personalized medicine

- Clinical utility remains limited
- Reliable estimates?

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Main Results

- While no SNP was linked to DFS, specific variants were associated with an increased risk of metastasis and mortality from breast cancer. Interestingly, the same SNPs seemed to offer some protection against serious adverse events, such as bone fractures and cardiovascular complications.

Clinical Implications

- These results pave the way for more targeted therapy. We can now begin to consider how to use this genetic information to predict treatment response and personalize therapeutic strategies. This concerns not only the selection of adjuvant treatment but also the monitoring and management of long-term side effects

Future Perspectives

- Looking to the future, it is essential that our research focuses on how to integrate these SNPs into clinical practice. There is vast potential in using these genetic markers to refine our clinical decisions, thereby optimizing the benefits of endocrine treatment and minimizing risks for patients. Further studies are necessary to understand how these SNPs can be used to personalize adjuvant therapy and manage side effects.

Open Questions and Directions for Future Research

- Could aromatase SNPs influence the effectiveness of bone-targeting agents like denosumab and zometa in breast cancer treatment by predicting metastasis risk and identifying patients most likely to benefit from bone therapies?
- Might the role of aromatase SNPs in predicting treatment response sharpen the therapeutic impact of abemaciclib and ribociclib in ER+/HER2- breast cancer adjuvant therapy, taking into account side effects and individual response?
- How might aromatase SNP profiling inform the selection between fulvestrant and AI in combination with CDK4/6 inhibitors in the metastatic setting, with the potential to optimize treatment efficacy and minimize toxicity?