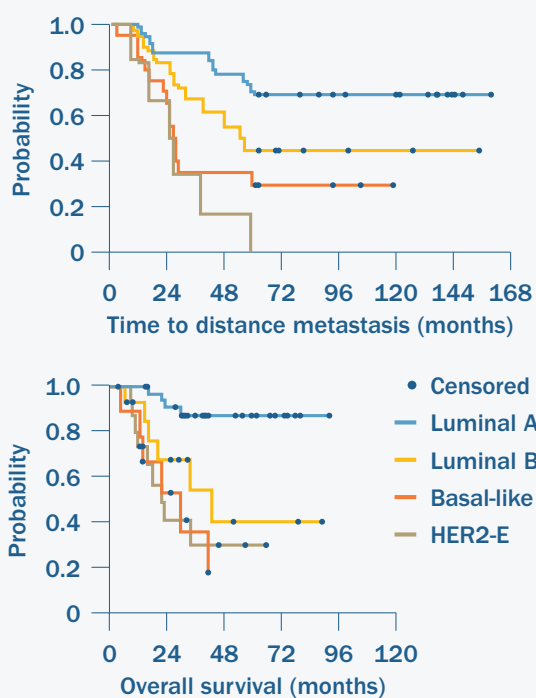


Breast cancer consists of many diseases. This heterogeneity is visible at the histological, clinical, genetic and genomic level. Genomic studies have identified four intrinsic subtypes of breast cancer: basal-like, luminal A and B, and HER2-enriched. The basal-like tumours are identified by high expression of *KRT5/6A*, *ID4*, and *FOXC1* (basal epithelial-like cluster). The luminal epithelial-like cluster is characterized by high expression of *ER*, *GATA3*, *XBP1*, and *FOXA1*. Luminal A tumours have the highest expression of luminal epithelial genes when compared

with luminal B tumours; luminal A and B tumours show, respectively, low and high proliferation rates. The HER2-enriched subtype, although expressing the luminal-epithelial cluster, is defined by amplification of genes on 17q12 including *HER2/ERBB2*. Recent studies have described the somatic mutations and DNA copy-number landscape of breast cancers, showing a good concordance between these genetic alterations and the genetic intrinsic subtypes. Here, we present an overview of the common genetic and genomic events seen in breast tumours.

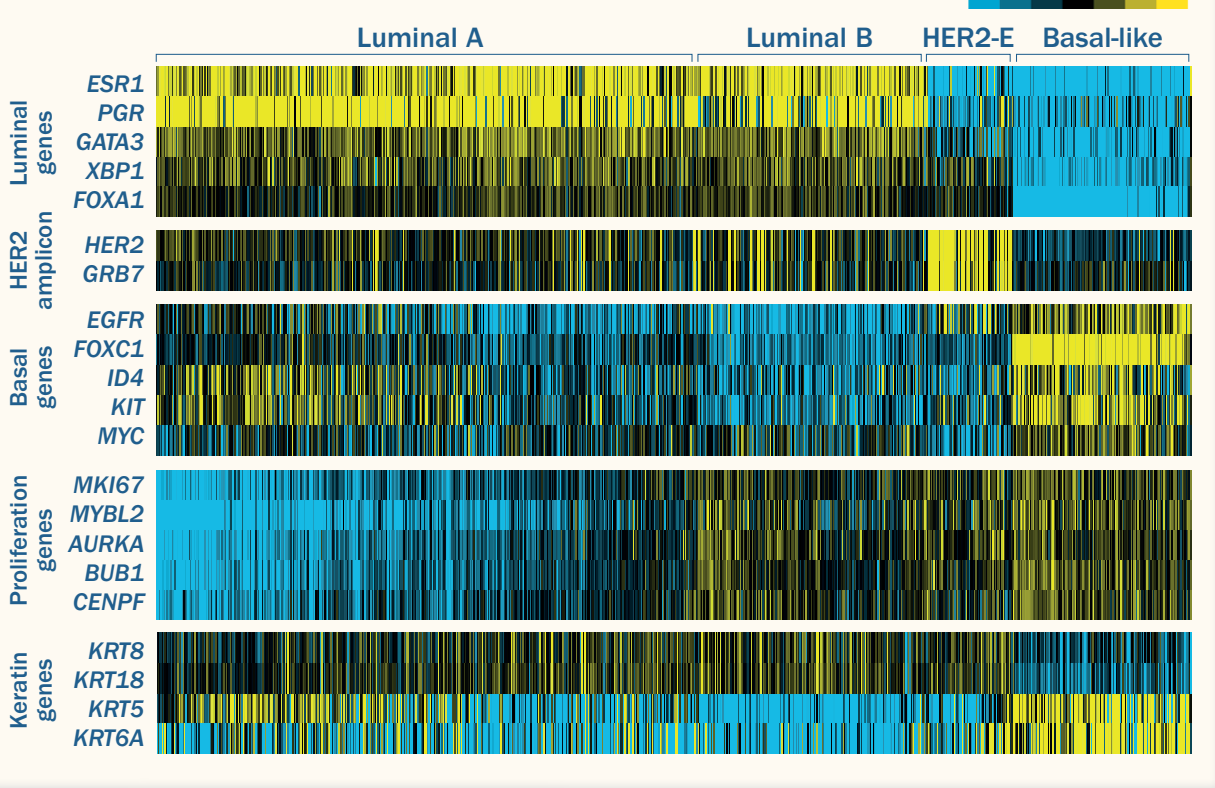
Clinical outcomes

The intrinsic subtypes of breast cancer can predict prognosis.^{1,2} Luminal A tumours tend to have the most favourable outcomes, while luminal B, HER2-enriched, and basal-like tumours have worse prognosis. At the clinical level, there is correlation between the three established clinical biomarkers—ER, PR, and HER2—and the intrinsic subtypes. Luminal A tumours tend to be ER+, PR+, HER2-. Luminal B tumours are likely to be ER+, PR+/-and sometimes HER2+.³ The HER2-enriched tumours are usually HER2+/ER-. The basal-like subtype tends to be triple negative (ER-, PR-, HER2-). Despite this correlation, the intrinsic subtypes cannot be accurately identified using these markers.³ Nonetheless, most luminal A and B tumours are ER+ and/or PR+, and thus candidates for endocrine therapy; most HER2-enriched cancers are HER2+ and thus candidates for anti-HER2 therapies, and most basal-like tumours are ER-, PR-, and HER2- and therefore candidates for chemotherapy regimens.



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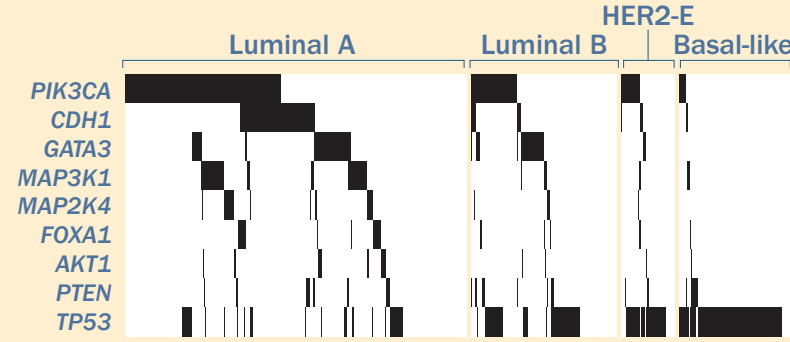
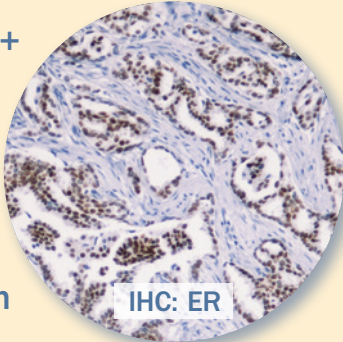
Gene profile



Breast-tumour samples from TCGA (n=792) were ordered according to intrinsic subtype and then by correlation to the subtype centroid.⁴ Gene-expression data for selected genes are shown. Yellow: higher than median gene expression; black: median; blue: lower than median.

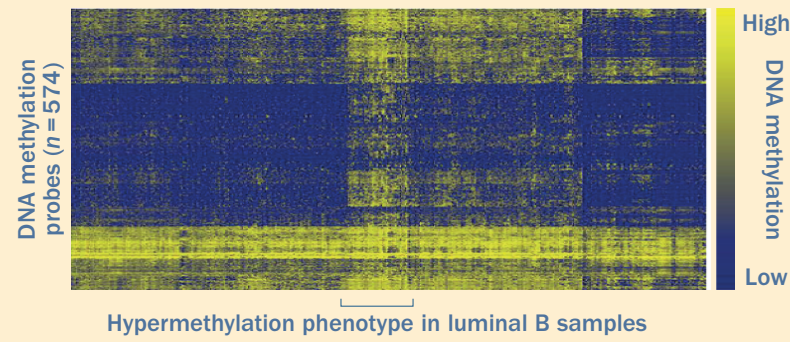
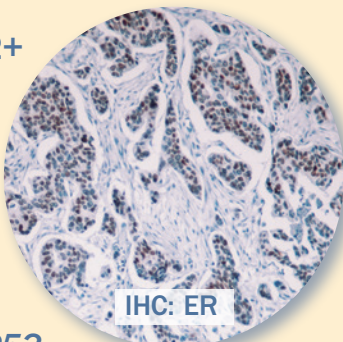
Luminal A

- 90% ER+, 89% PR+, 14% HER2+
- Mostly diploid; few copy number changes; 1q gain and 16q loss
 - Low pathological grade; high morphological differentiation; low proliferation rates
 - Recurrently mutated genes (>5%): *PIK3CA*, *CDH1*, *MAP3K1*, *GATA3*, *MAP2K4*, *FOXA1*, *TP53*, *RUNX1*, *CBFB*, *NBL1*, *CTCF*, *NCOR1*, *PTEN*, *CDKN1B*, *AKT1*, *TBX3*, *ARID1A*, and *NF1*
 - Typically responsive to endocrine therapy
 - Usually less responsive to (neo)adjuvant chemotherapy
 - Highest number of recurrently mutated genes, but the lowest total number of mutations and copy number changes, suggesting that these alterations are likely to be driver mutations (see figure, black line indicates a non-silent mutation)

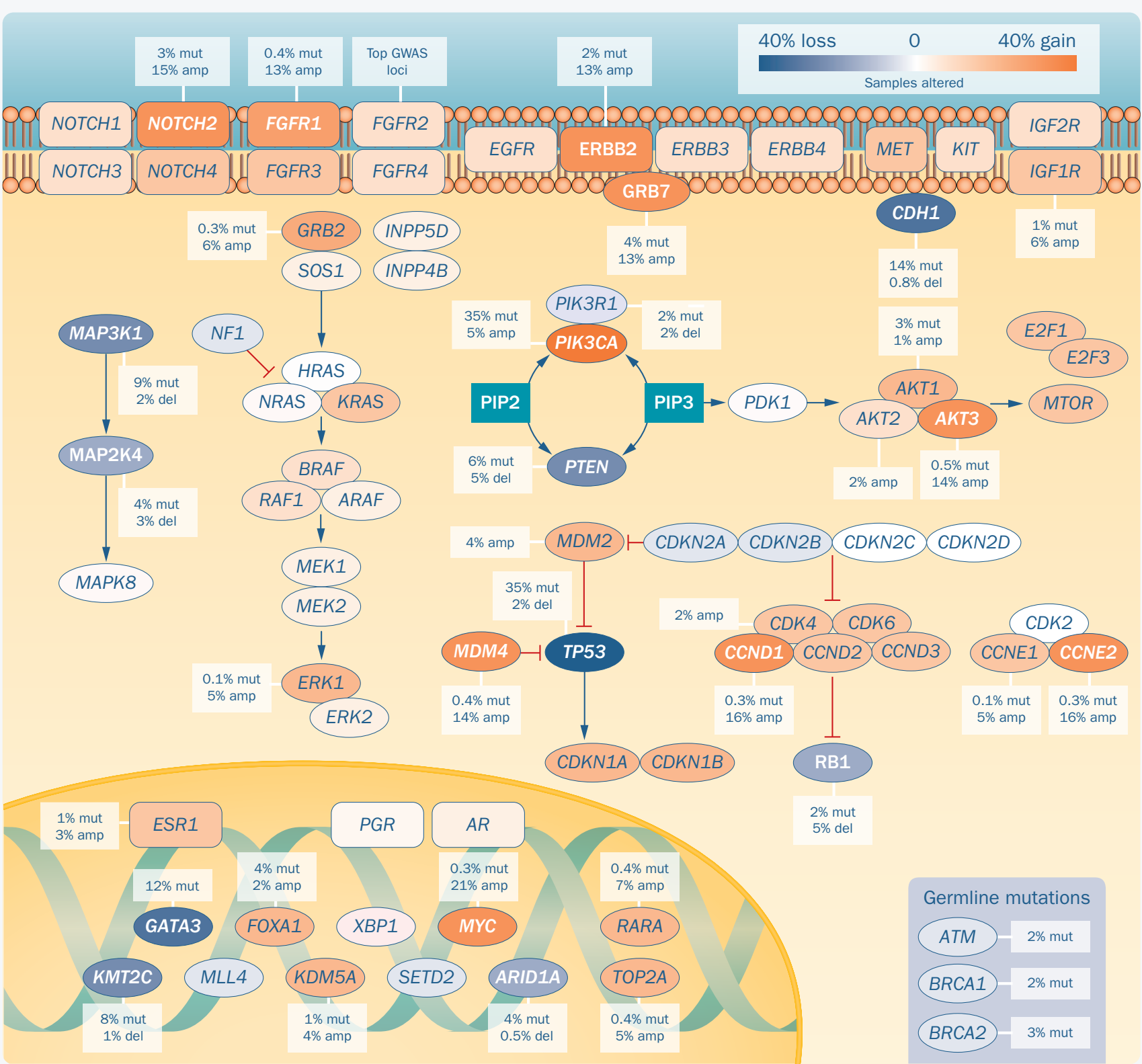


Luminal B

- 98% ER+, 82% PR+, 24% HER2+
- Mostly aneuploid, with many high-level focal amplifications (11q13 [Cyclin D1, 56%]; 8p11–12 [FGFR1, 23%])
 - Recurrently mutated genes: *PIK3CA*, *GATA3*, *PTEN*, and *TP53*
 - The quantitative level of PR is lower in luminal B relative to luminal A, while Ki-67 is higher in luminal B relative to luminal A³
 - Typically responsive to endocrine therapy, possibly less so than luminal A cancers
 - Higher pCR rate to neoadjuvant chemotherapy⁹ and possibly more sensitive to adjuvant chemotherapy than luminal A cancers
 - A subset of luminal B tumours have a hypermethylated phenotype (see figure),⁴ based on genome-wide DNA methylation patterns



Hypermethylation phenotype in luminal B samples



Common genetic alterations

TCGA data on breast tumour DNA copy number and somatic mutations were used to identify the frequency of each genetic alteration across 792 patients (all cancer subtypes).⁴

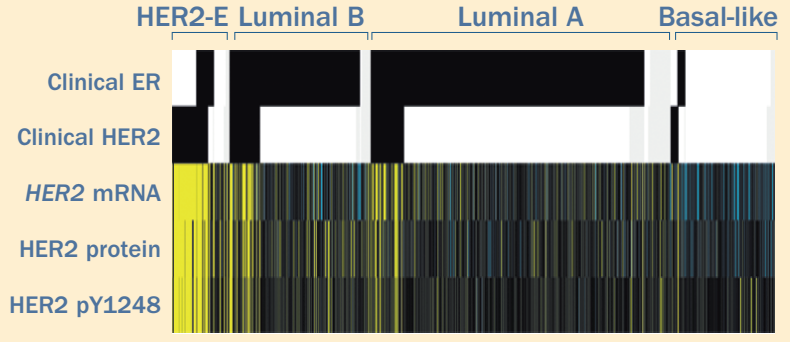
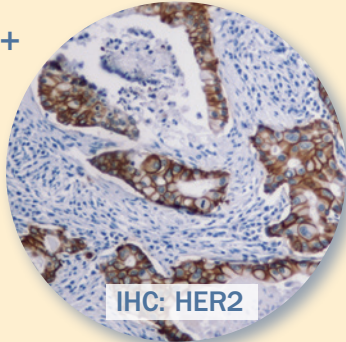
Each gene is shaded according to the overall frequency of alteration. Orange indicates a high level of amplification and/or likely gain-of-function mutations; blue represents homozygous deletions and/or likely loss-of-function mutations.

Three germline mutation rates are shown—taken from a subset of 500 TCGA samples previously published.⁴

Biomarker	Potential treatment	Evidence
Luminal A and B ER+ and/or PR+ by IHC PIK3CA mutation FGFR1 amplification Germline BRCA1/BRCA2 variants GATA3 mutation MDM2 amplification TP53 mutation HER2 mutation CCND1/CDK4/CDK6 amplified AKT1 mutation IGF1R amplification	Endocrine therapy PI3K inhibitors FGFR inhibitors PARP inhibitors Endocrine therapy MDM2 inhibitors Sensitivity to chemotherapy HER2 inhibitors CDK4/6 inhibitors AKT inhibitors IGFR inhibitors	Meta-analysis Data from phase I and II trials Data from phase I and II trials Data from phase I and II trials Retrospective analysis of trials Preclinical evidence Retrospective analysis of trials Preclinical evidence Preclinical evidence Preclinical evidence Preclinical evidence
HER2-enriched HER2 amplification or HER2 IHC+ HER2 mutation PIK3CA mutation PTEN mutation/loss PIK3R1 mutation FGFR4 amplification	HER2 inhibitors HER2 inhibitors PI3K inhibitors PI3K/mTOR inhibitors PI3K inhibitors FGFR inhibitors	Data from phase III trials Preclinical evidence Data from phase I and II trials Retrospective analysis of trials Preclinical evidence Preclinical evidence
Basal-like Germline BRCA1/BRCA2 mutation NOTCH1/NOTCH3 amplification/mutation AKT3 amplification EGFR amplification NF1 deletion, KRAS amplification TP53 mutation PIK3R1/PTEN/INPP4B mutation/loss MET amplification/mutation	PARP inhibitors γ-Secretase inhibitors AKT inhibitors EGFR inhibitors MEK inhibitors Sensitivity to chemotherapy PI3K inhibitors MET inhibitors	Data from phase I and II trials Preclinical evidence Preclinical evidence Preclinical evidence Phase I and II trials in other diseases Retrospective analysis of trials Preclinical evidence Preclinical evidence

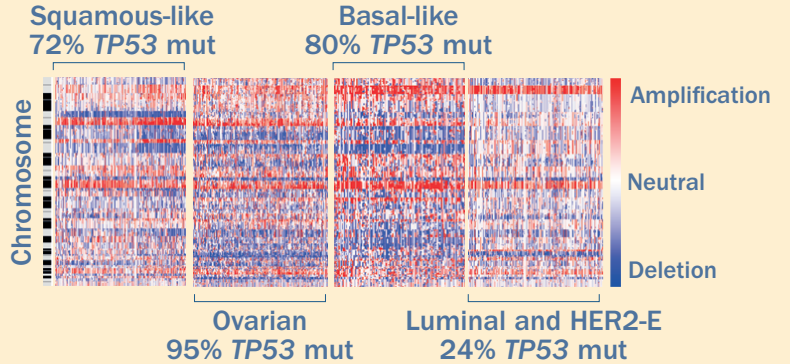
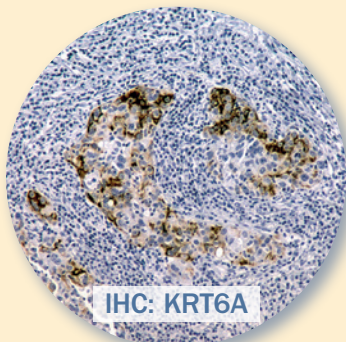
HER2-enriched

- 38% ER+, 20% PR+, 72% HER2+
- High levels of *HER2/ERBB2* amplification
 - Mostly aneuploid with high chromosomal instability
 - Highest single nucleotide mutation rate,⁴ but small list of recurrently mutated genes (*TP53* [71%] and *PIK3CA* [35%])
 - Mostly high pathological grade, typically ER- (62%)
 - High rate of brain metastases
 - Typically responsive to (neo)adjuvant trastuzumab in combination with chemotherapy⁶
 - Sensitive to adjuvant anthracyclines⁷ and taxanes⁸
 - HER2-enriched tumours that are also clinically HER2+ show high levels of HER2 protein and phosphoprotein suggesting active HER2 signalling (see figure)



Basal-like

- 8% ER+, 7% PR+, 7% HER2+
- Includes 70–80% of TNBC¹⁰
 - High metastasis rate¹¹
 - Associated with younger age; high frequency in those of African descent¹²
 - Associated with *BRCA1* germline mutations²
 - *TP53* is the only recurrently mutated gene (>10%)
 - Highest pCR rate to neoadjuvant chemotherapy⁹
 - TILs are prognostic within this subtype¹³
 - In a 12 tumour-type analysis, the basal-like subtype formed a unique group¹⁴ (distinct from other breast cancers), showing similar characteristics to ovarian cancer, squamous cancers of the lung, head and neck, with frequent *TP53* mutations, amplification of 3q, loss of 4q and 5q (see figure)



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Abbreviations

amp	amplification
APOBEC	apolipoprotein B mRNA editing enzyme
ER	oestrogen receptor
ER+	oestrogen receptor positive
ER-	oestrogen receptor negative
HER2+	HER2 positive
HER2-	HER2 negative
HER2-E	HER2-enriched molecular subtype
IHC	immunohistochemistry
KRT	cytokeratin
mut	mutation
pCR	pathological complete response
PR	progesterone receptor
PR+	progesterone receptor positive
TCGA	The Cancer Genome Atlas
TIL	tumour-infiltrating lymphocyte
TNBC	triple-negative breast cancer

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