Ki67:
Can it assist in triage of patients to receive NET?

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Ki67

Do you do Ki67 testing:

A. on all breast cancers

B. on all ER+ breast cancers

C. on selected ER+ breast cancers

D. Never

Ki67: intrinsic subtypes

- Proliferation signatures are key drivers in molecular subtyping of breast cancer
- Cheang et al., JNCI 2009;101:736-50
- 144 Luminal A & B cancers defined by GEP
- Optimal Ki67 cut point 13.25%; rounded to 14%
- Luminal B group defined by Ki67 > 14% had worse BCSS (HR 1.84) and relapse free survival (HR 1.43)
- **False positive and false negative rate 25%**

- MKI67 included in Oncotype Dx and PAM50

Ki67: prognostic factor

- Ki67 and other markers of proliferation associated with outcome in ER +ve/ HER2-ve tumours only
- Aleskandarany, Breast Ca Res 2012
- Count 1000 cells from ‘hot-spots’
- 10% optimal cut-off for ER+/ HER2- tumours
- BCSS HR=2.5; DMFS HR=2.2
- Independent on multivariate analyses; Ki67 highest HR
- Higher cut-off for HER2+ (75%) and TN tumours (70%); no association with outcome
- Similar findings from SEARCH data (Ali, BJC 2012)

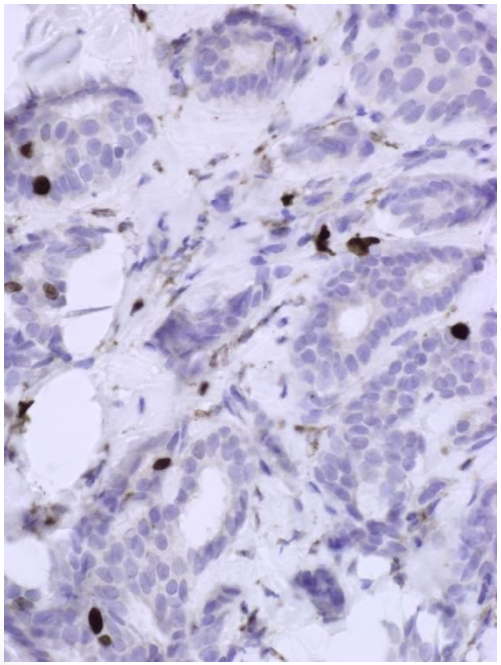
Ki67: predictive factor

Hormone therapy

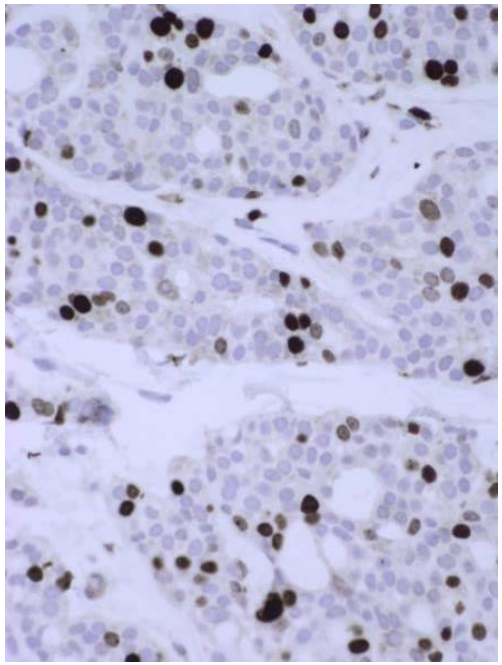
- Baseline Ki67 – high levels associated with shorter DFS; no clear association with response to hormonal therapy
- Neoadjuvant hormonal therapy – Ki67 level during or after treatment more predictive of outcome than pre-RX levels
- IMPACT trial – high Ki67 after 2 weeks of Rx associated with lower RFS
- HOWEVER 15% of patients with an initial drop showed a rebound in Ki67 level at 12 weeks

Ki67: reporting issues

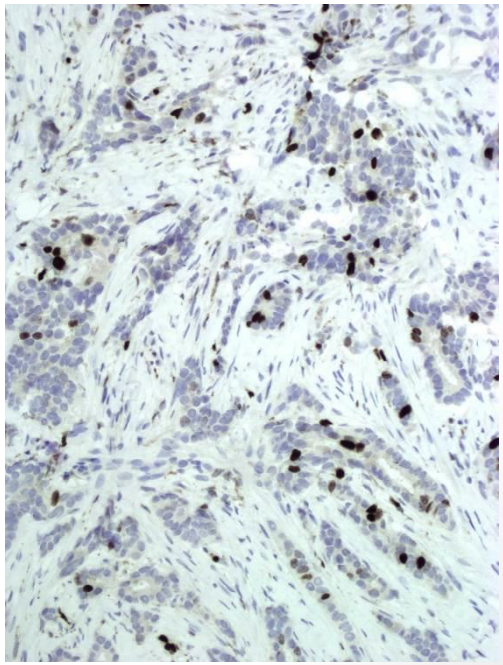
- Any intensity regarded as positive staining
- Heterogeneity common
- Increase in Ki67 expression at periphery of tumour
- Presence of ‘hot spots’
- Average versus ‘hot spot’ count



3%



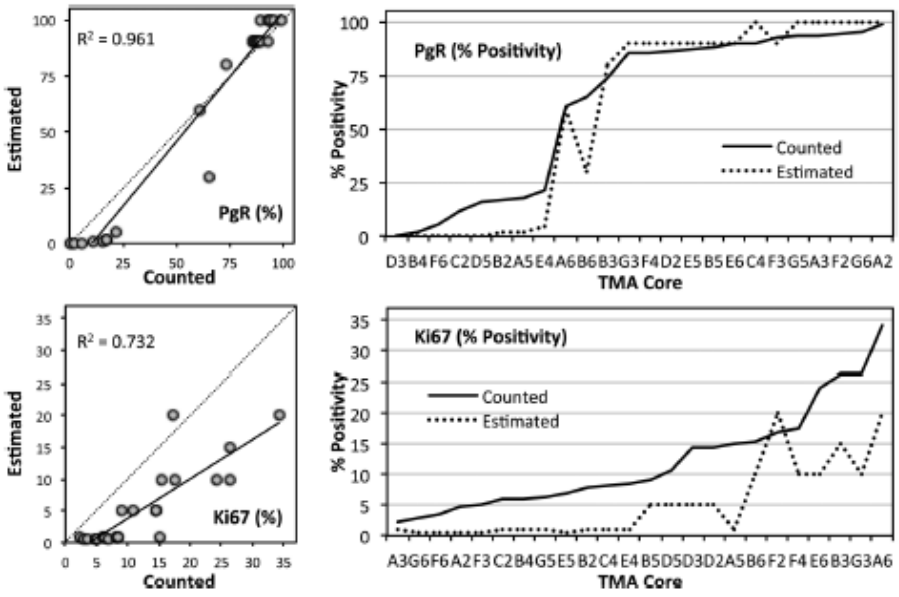
25%



14%

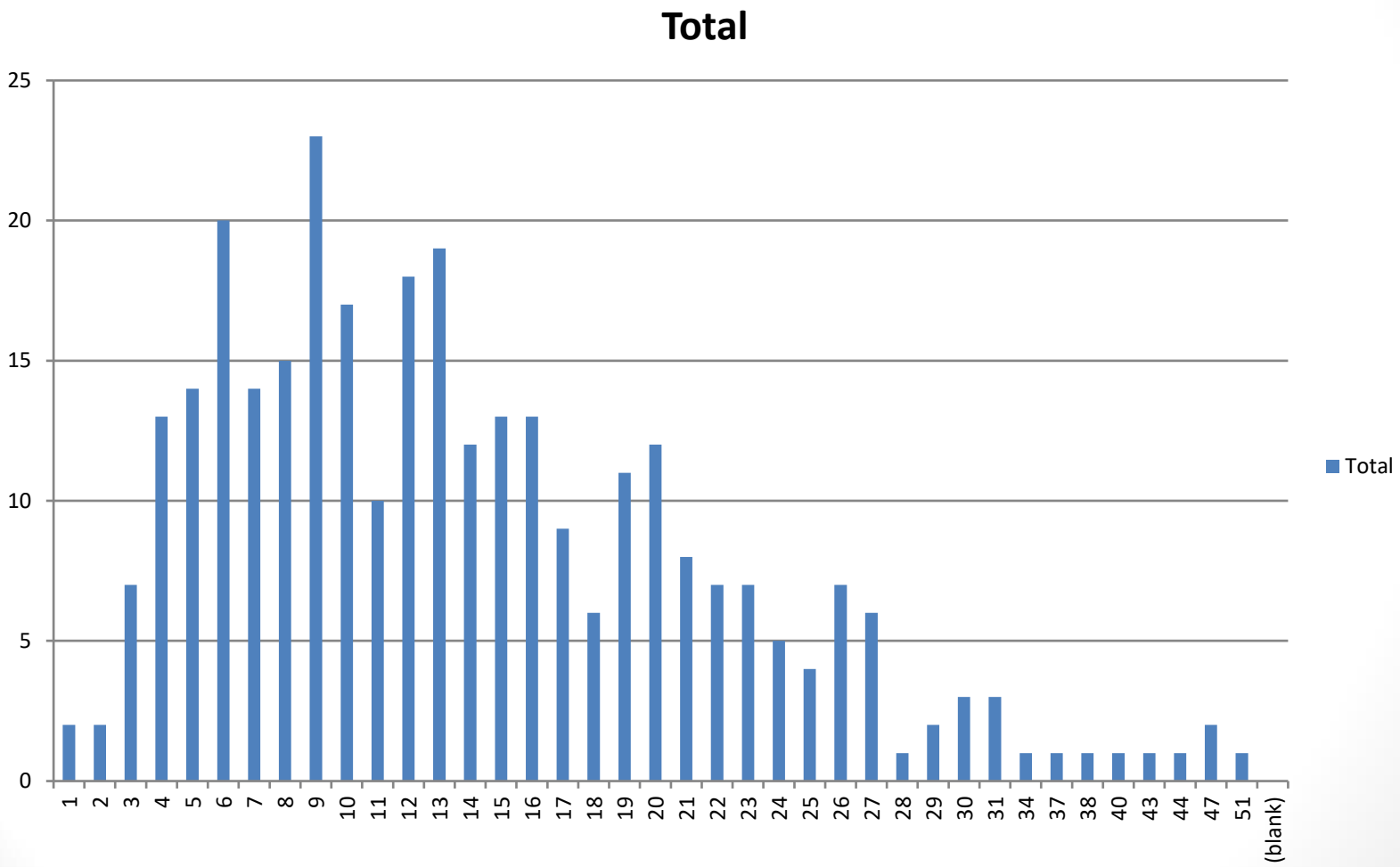
Ki67: reporting issues

- Major concerns with analytic validity of Ki67 IHC assessment
- Inconsistent cut-offs for positivity between guidelines (10%, 14%, 20%); value may be context dependent
- Visual estimates versus counting of cells
- Reproducibility poor especially for G2 tumours
- Role for image analysis software



Dodson et al., J Clin Path 2015

Ki67 reporting issues



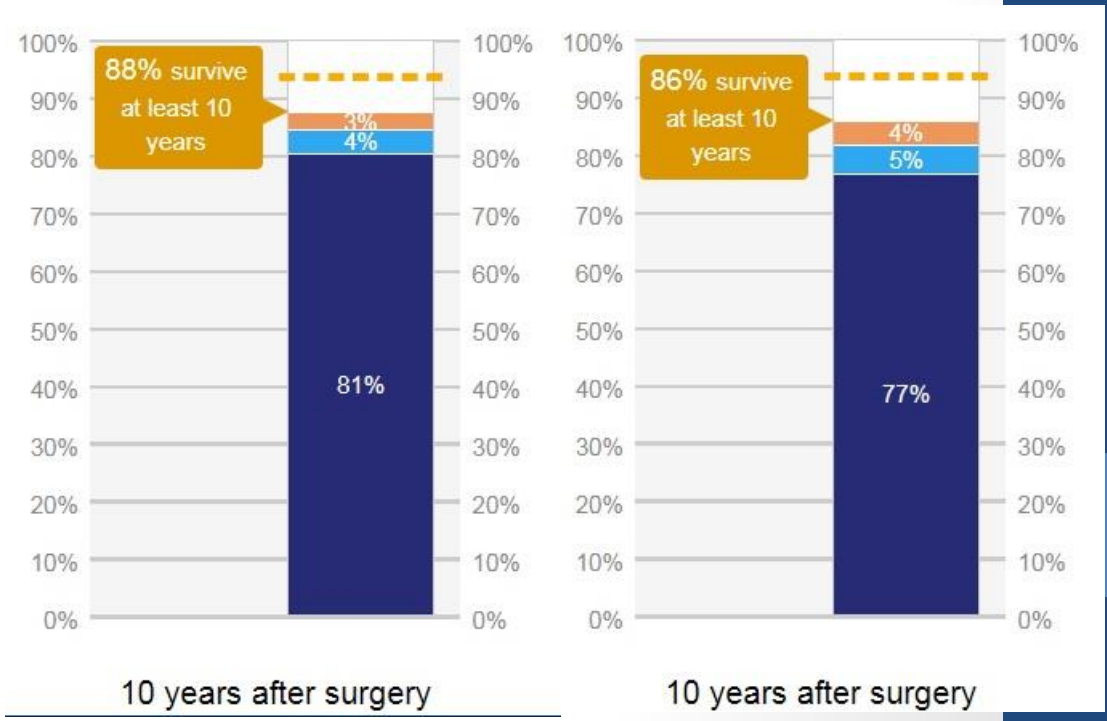
Ki67: reporting issues

- Which method do you use?
- Eyeballing – if using a single cut off can use at extremes with formal count in cases close to cut off
- Number of cell nuclei counted
- Original Ki67 working group guidelines recommend 500-1000 from at least 3 x40 fields
  - Dowsett et al., JNCI 2011;103:1656-664
- Newer method using Ki67 app
  - Estimate proportion of tumour with low/medium/high ki67 index
  - Count 1st 100 cells in up to 4 hpf representing different areas of ki67 expression
  - ICC for global weighted score 0.84
  - Leung et al. npj Breast Cancer 2016

Ki67: Predict

- PREDICT updated to include Ki67
- Use cut-off of >10%
- MDT – patients in the borderline group for chemotherapy benefit => Ki67
- Used to prioritise patients for early surgery vs bridging ET

56 year old female
Screen detected cancer
27 mm G2 1LN +ve
ER+/ HER2-
Change in chemo benefit
3% to 4%



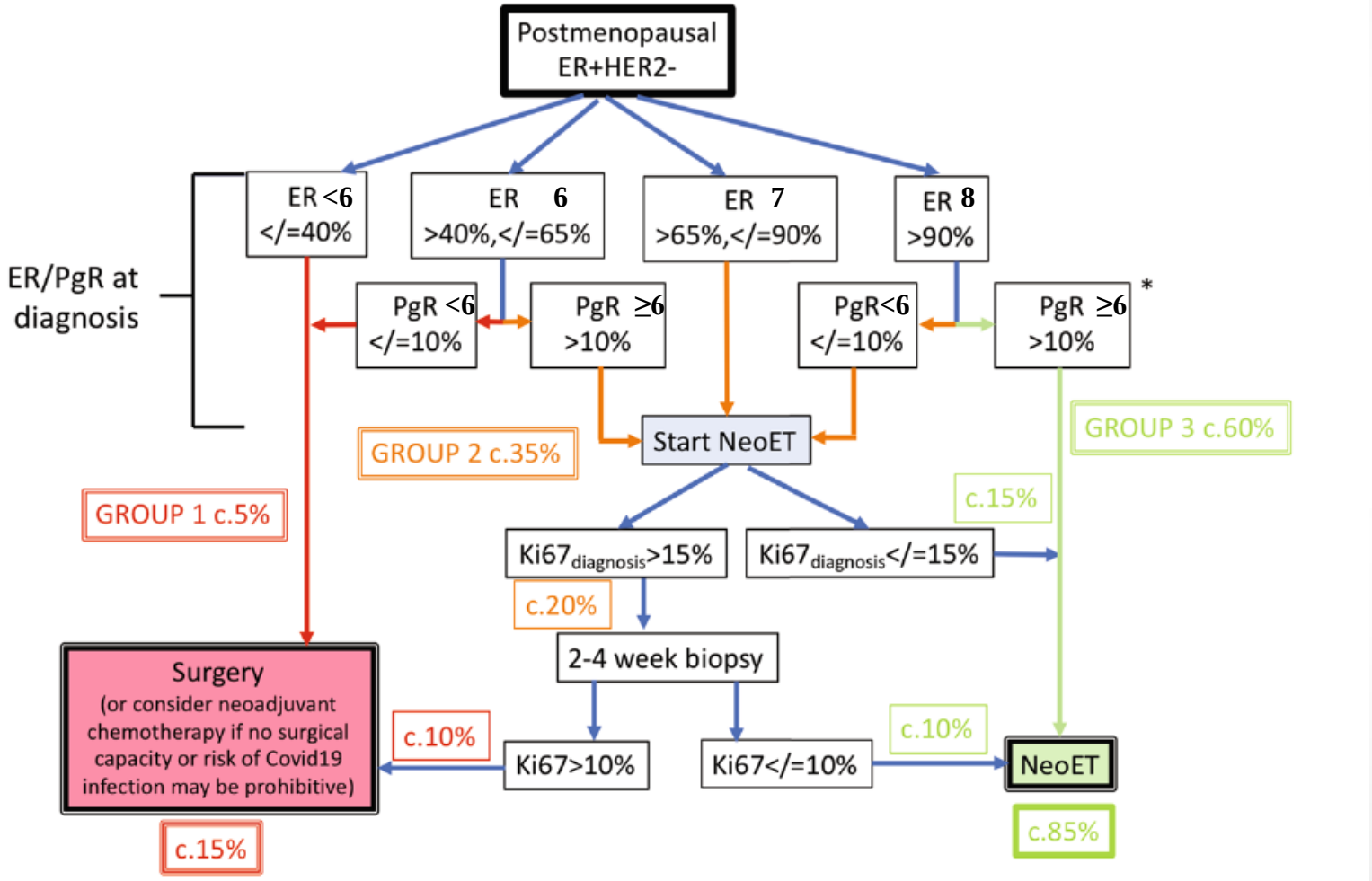
IHC4

- Developed by Cuzick et al., JCO 2011
- Algorithm using ER, PR, HER2 and Ki67 +/- clinico pathological variables to predict outcome in ER+ cancers treated with endocrine therapy
- ER10 – modified H score/ 30
- PR10 - % positive cells / 10
- HER2 – 0 negative, 1 positive
- Ki67 - % tumour cells staining (derived by image analysis)

$$IHC4 = 94.7 \times \{-0.100ER10 - 0.079PR10 + 0.0586HER2 + 0.240\ln(1+10 \times Ki67)\}$$

- Adds additional information compared with clinical variables alone
- Modest correlation with Oncotype RS (R=0.72)

Postmenopausal patients

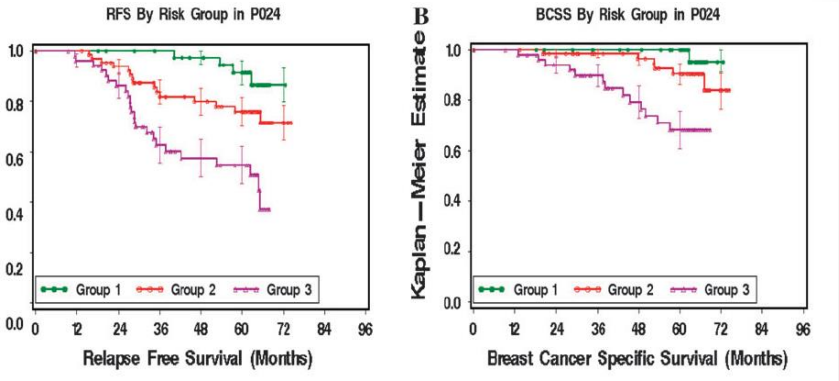


Dowsett et al., npj breast cancer 2020;6:21

PEPI

- Developed in P024 trial – 4 months NET
- Three risk groups:
  - Low – score 0
  - Intermediate – score 1-3
  - High – score ≥ 4

Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Pathological tumor size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7% (0–1†)	—	0	—	0
>2.7%–7.3% (1–2†)	1.3	1	1.4	1
>7.3%–19.7% (2–3†)	1.7	1	2.0	2
>19.7%–53.1% (3–4†)	2.2	2	2.7	3
>53.1% (>4†)	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0



Ellis et al., JNCI 2008;100:1380-88.