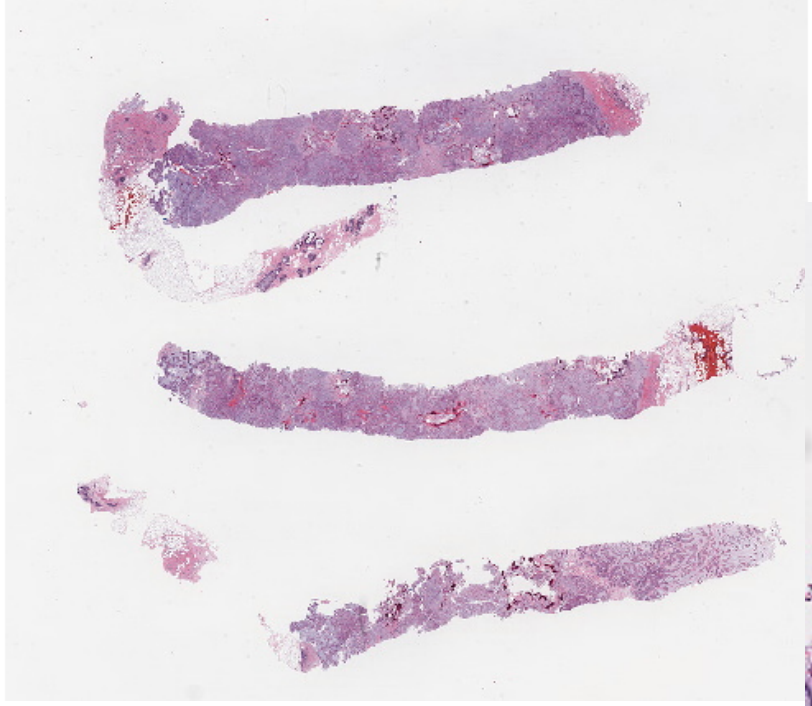
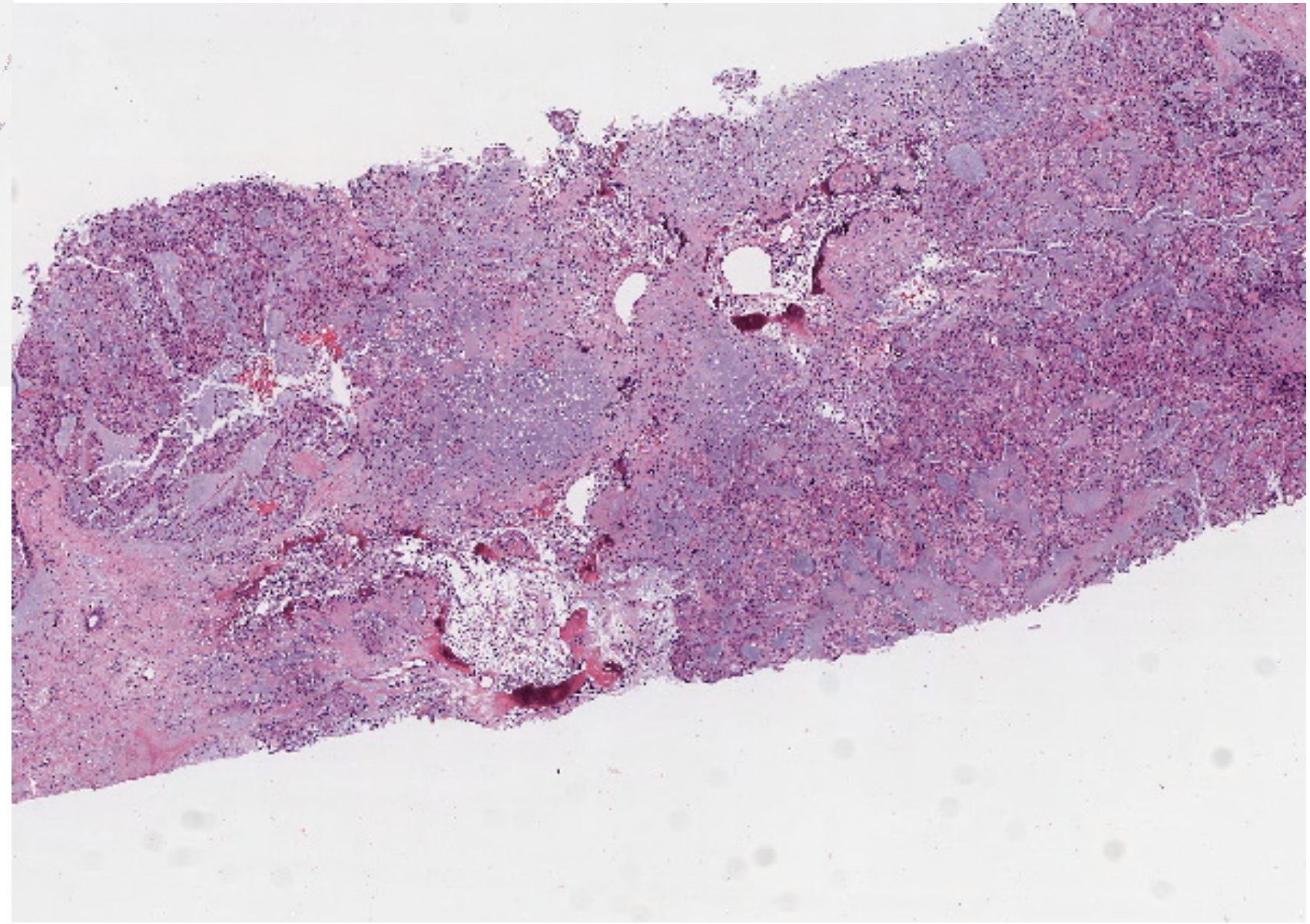
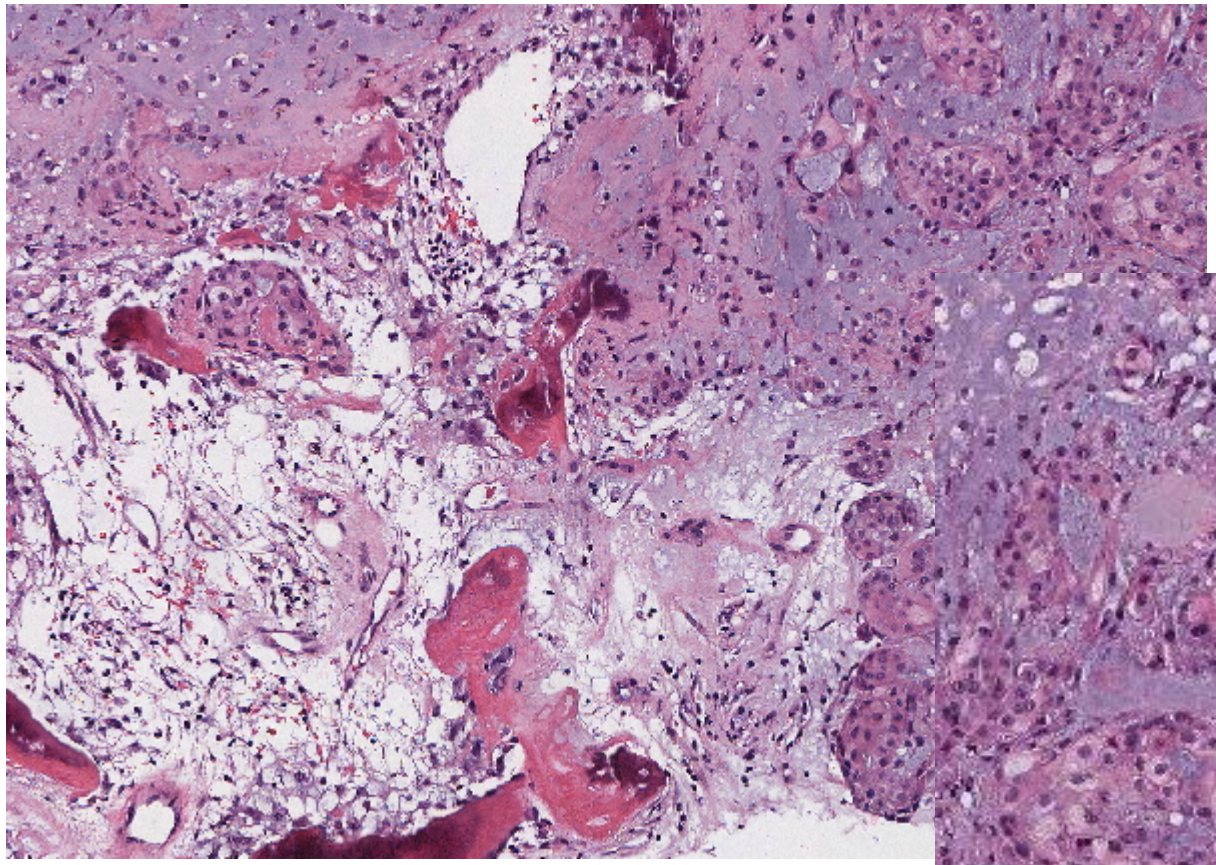
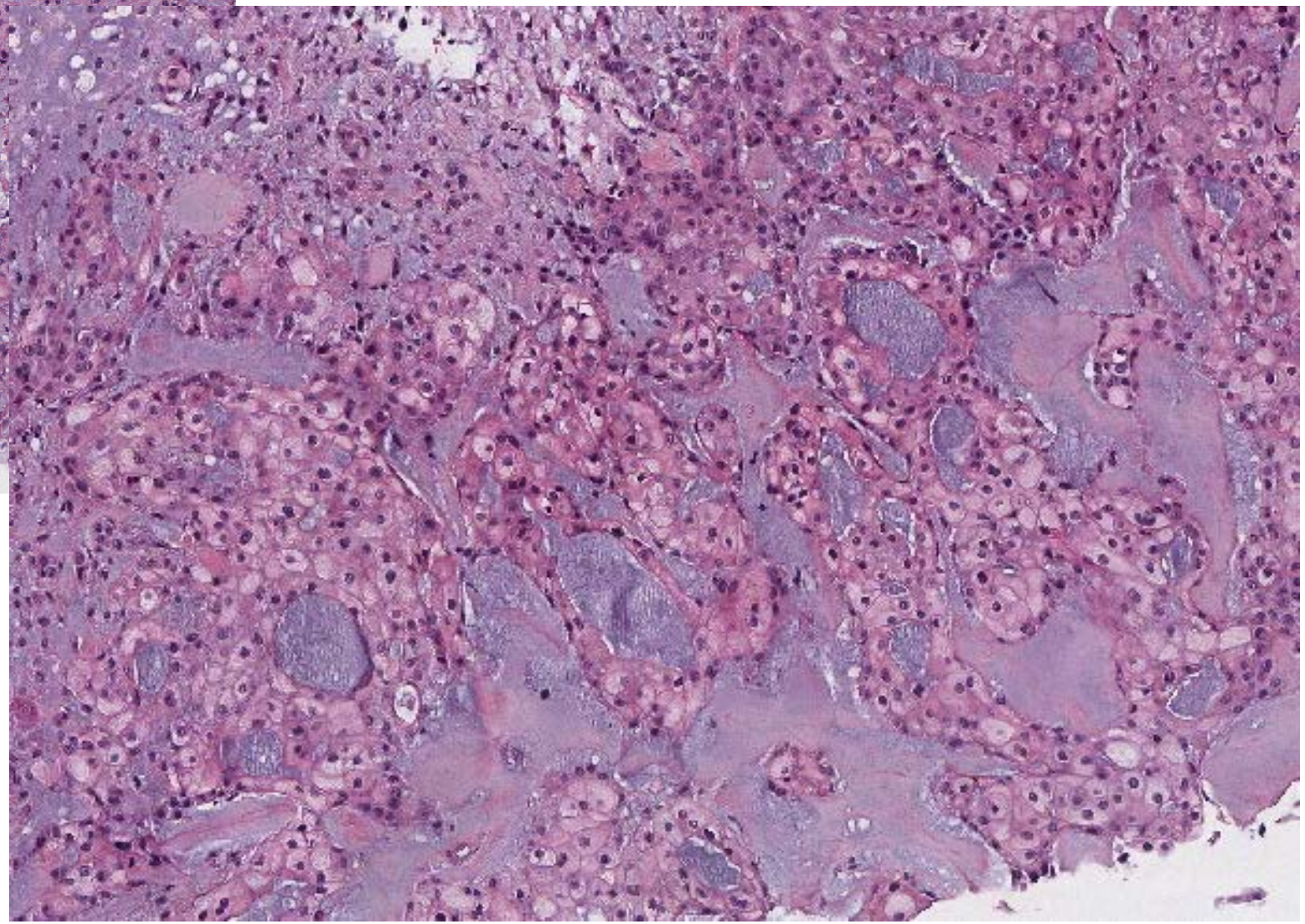
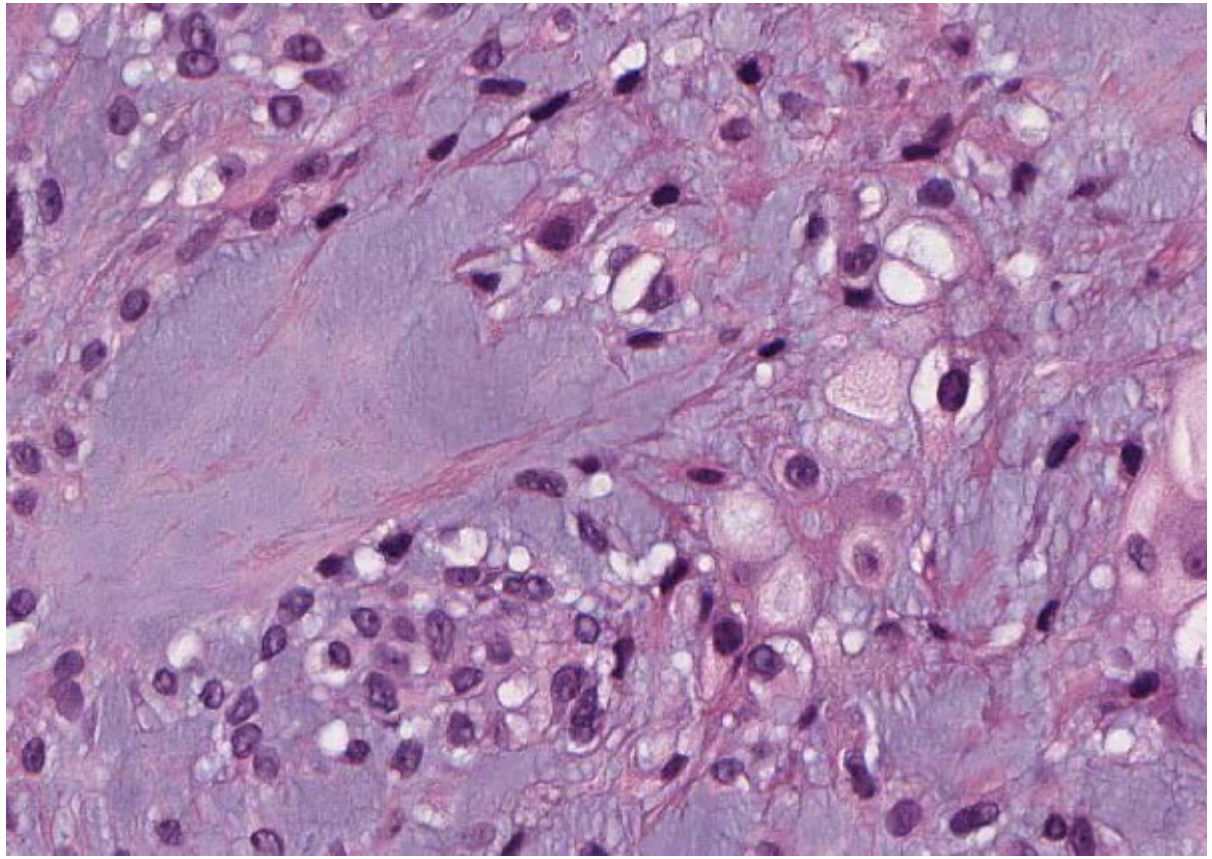
# Case 9

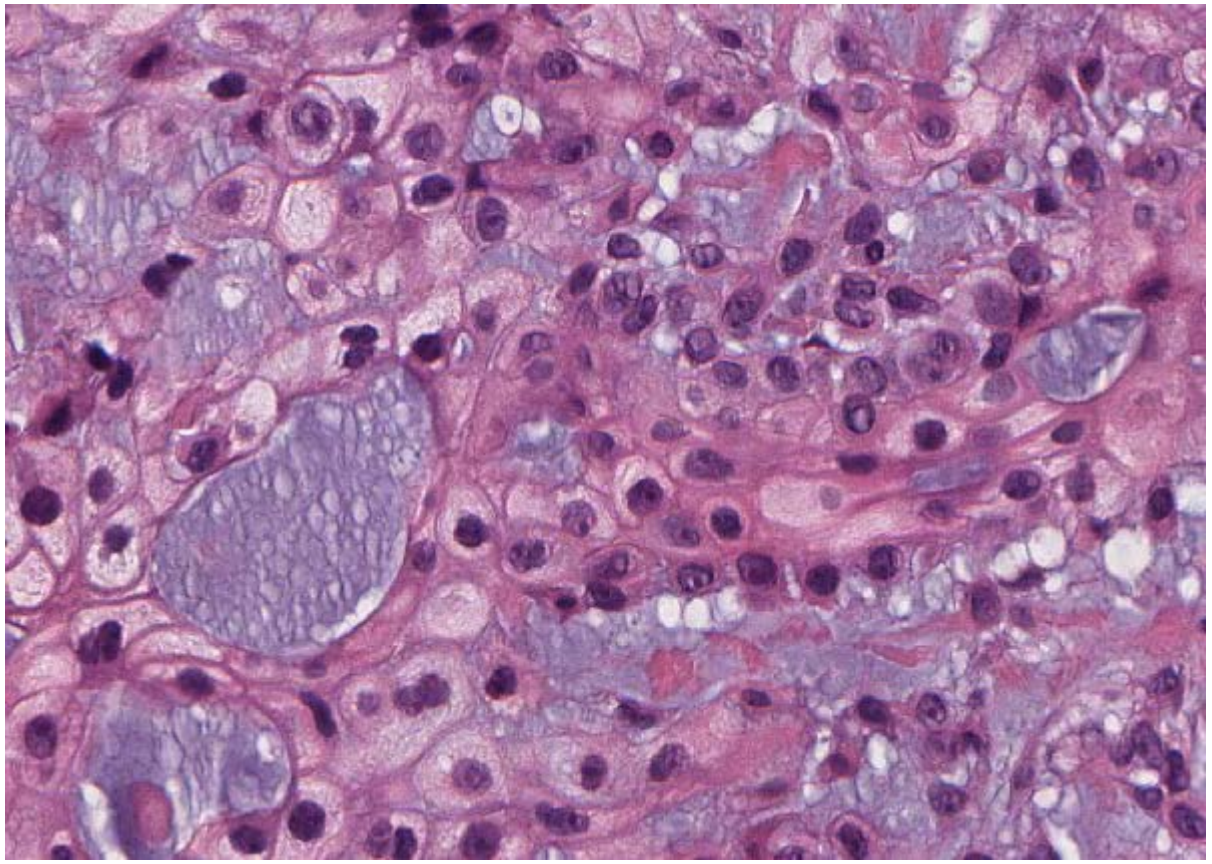




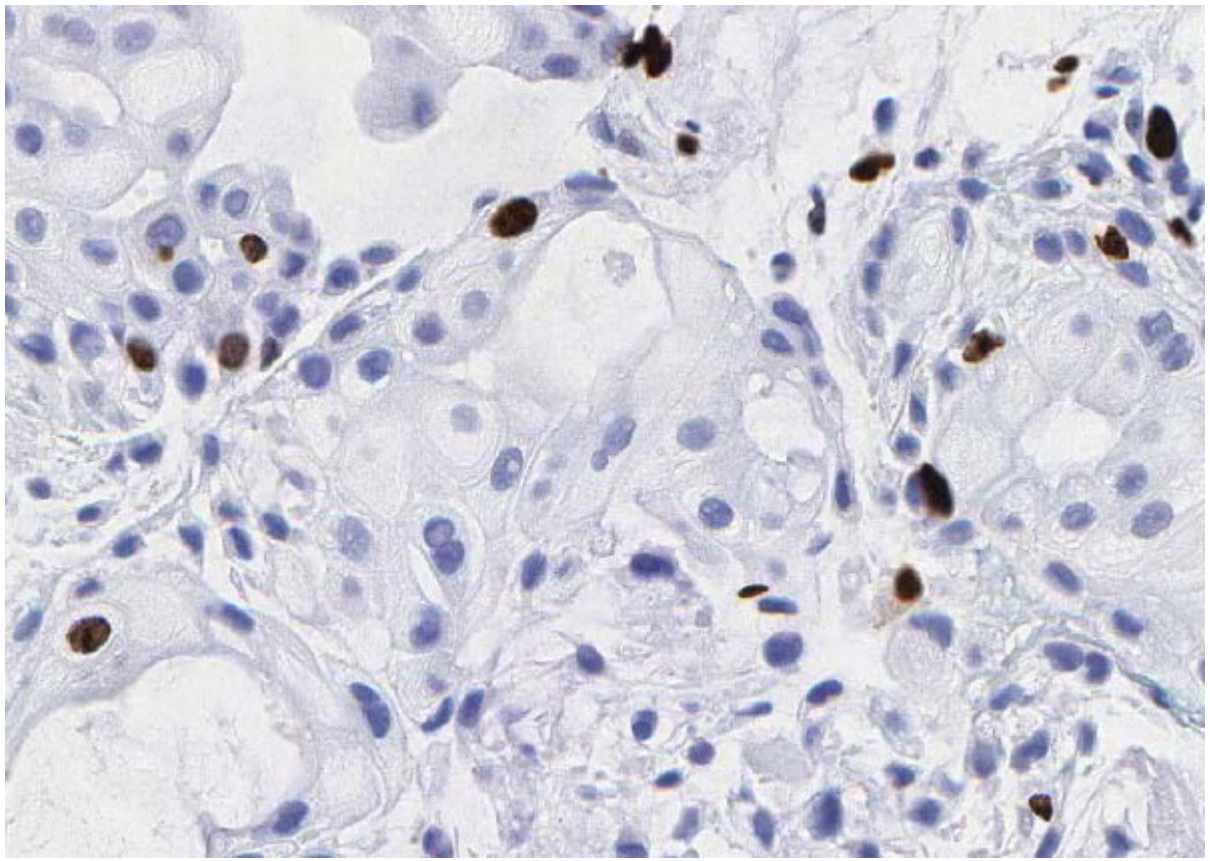


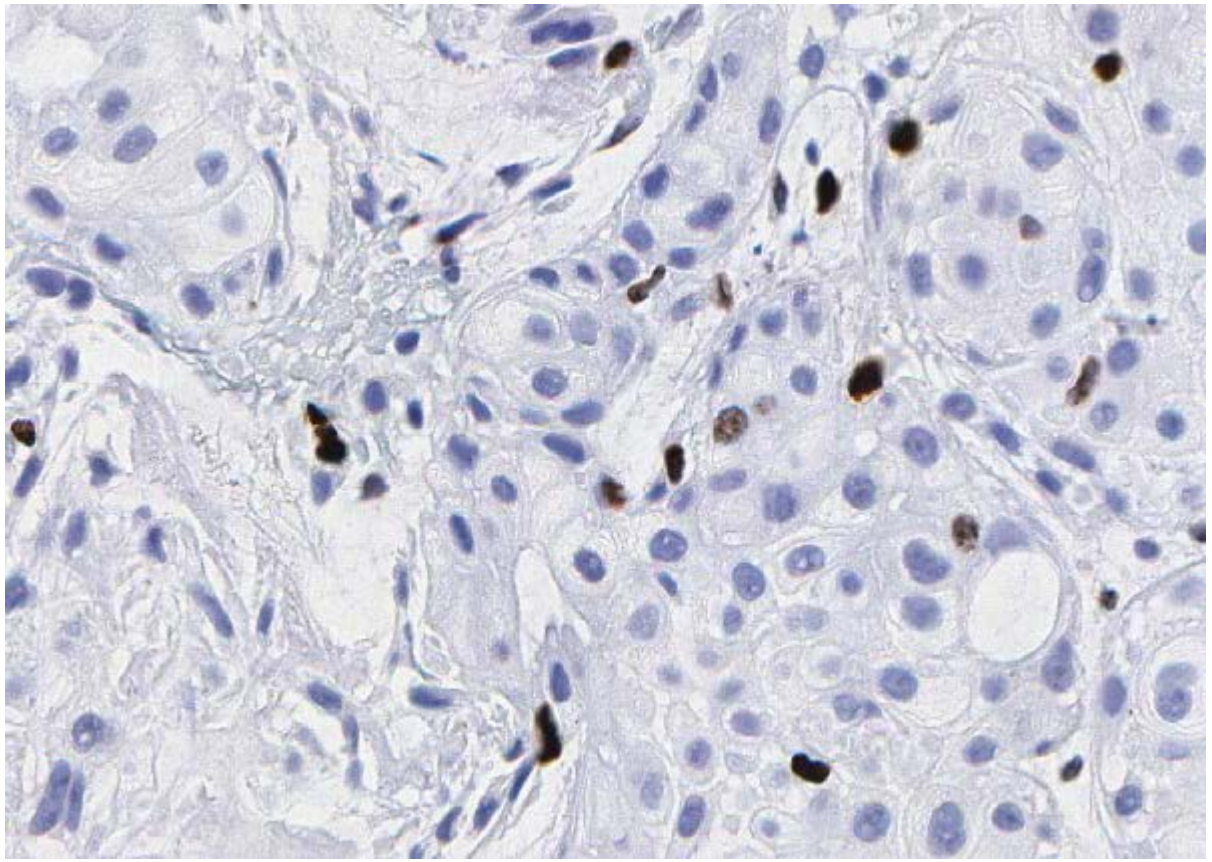






# Ki67

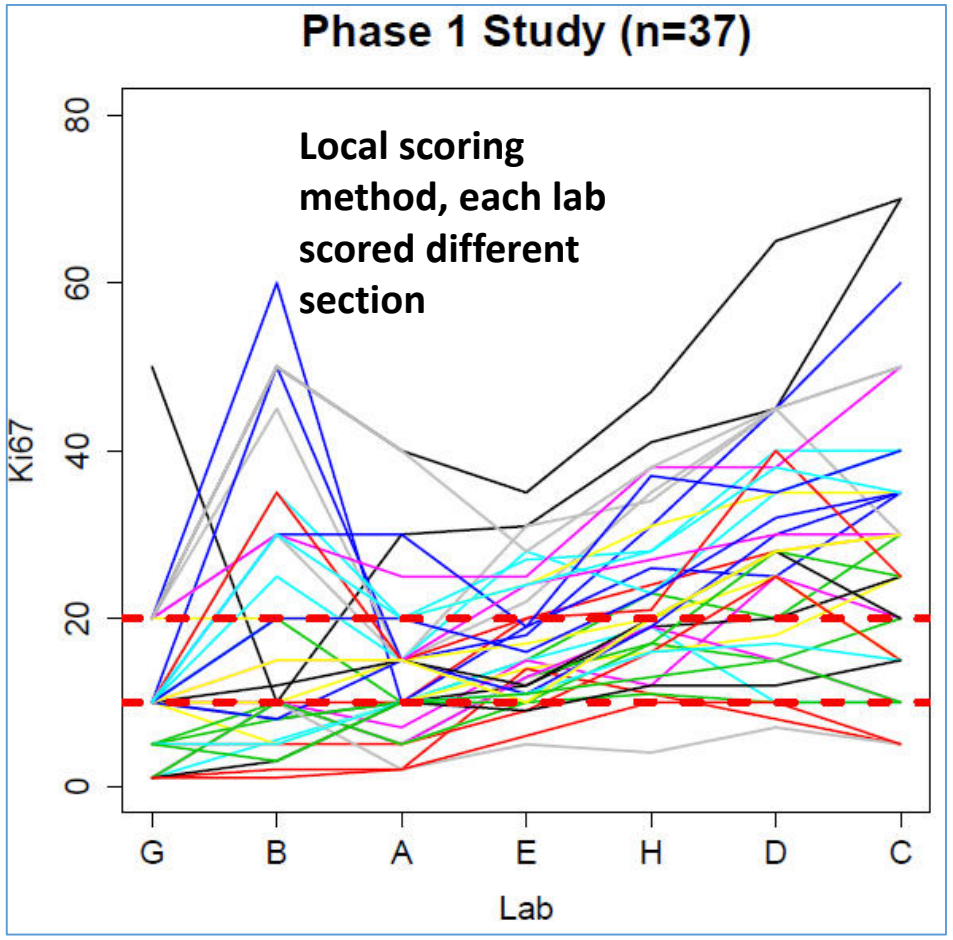


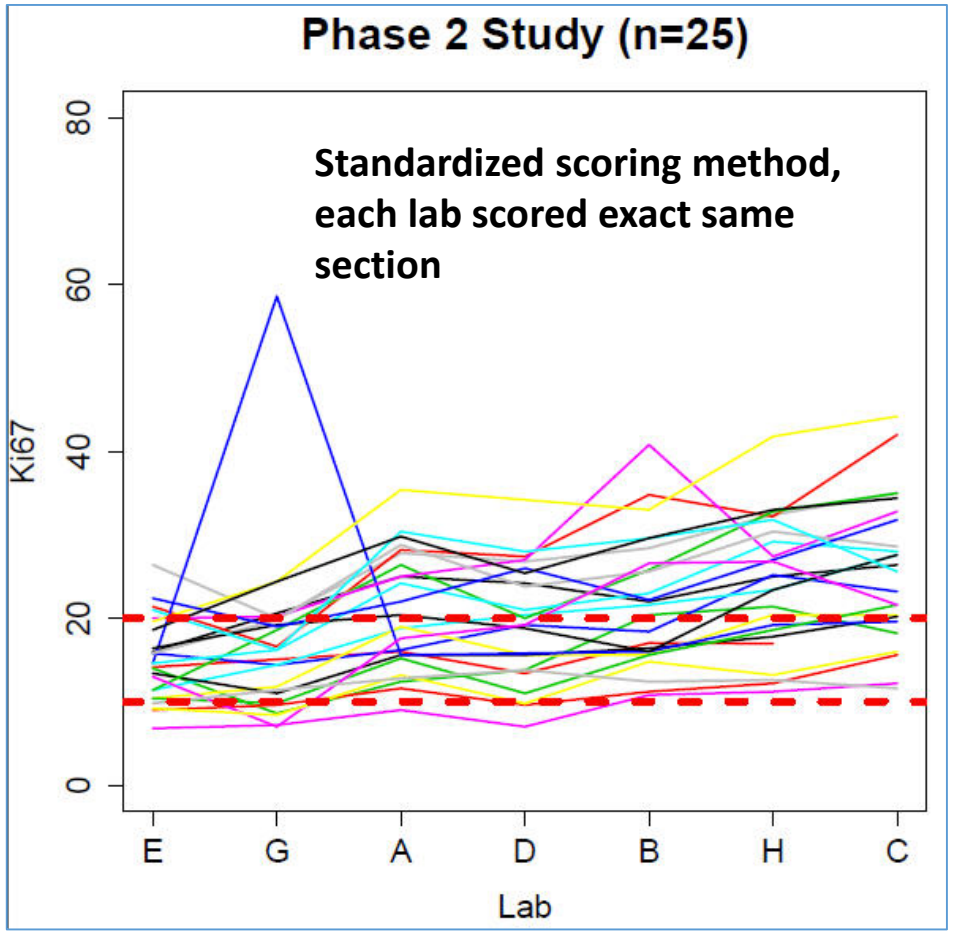


# Ki67

- Low proliferation rate
- Disagreement about how low?
- Sources of disagreement
  - Areas analyzed
  - Other factors

# Spaghetti plots: Ki67 of 10-20% (7 labs common to both phases)




**37 cases scored by ≥ 1 lab as 10-20%.**

**0 of the 37 scored by all labs as 10-20%.**

**25 cases scored by ≥ 1 lab as 10-20%.**

**0 of the 25 scored by all 7 labs as 10-20%.**

**1 case, scored by 5 of the 7 labs, was scored by all 5 labs as 10-20%.**

Nielsen TO et al SABCS 2013

# Assessment of concordance

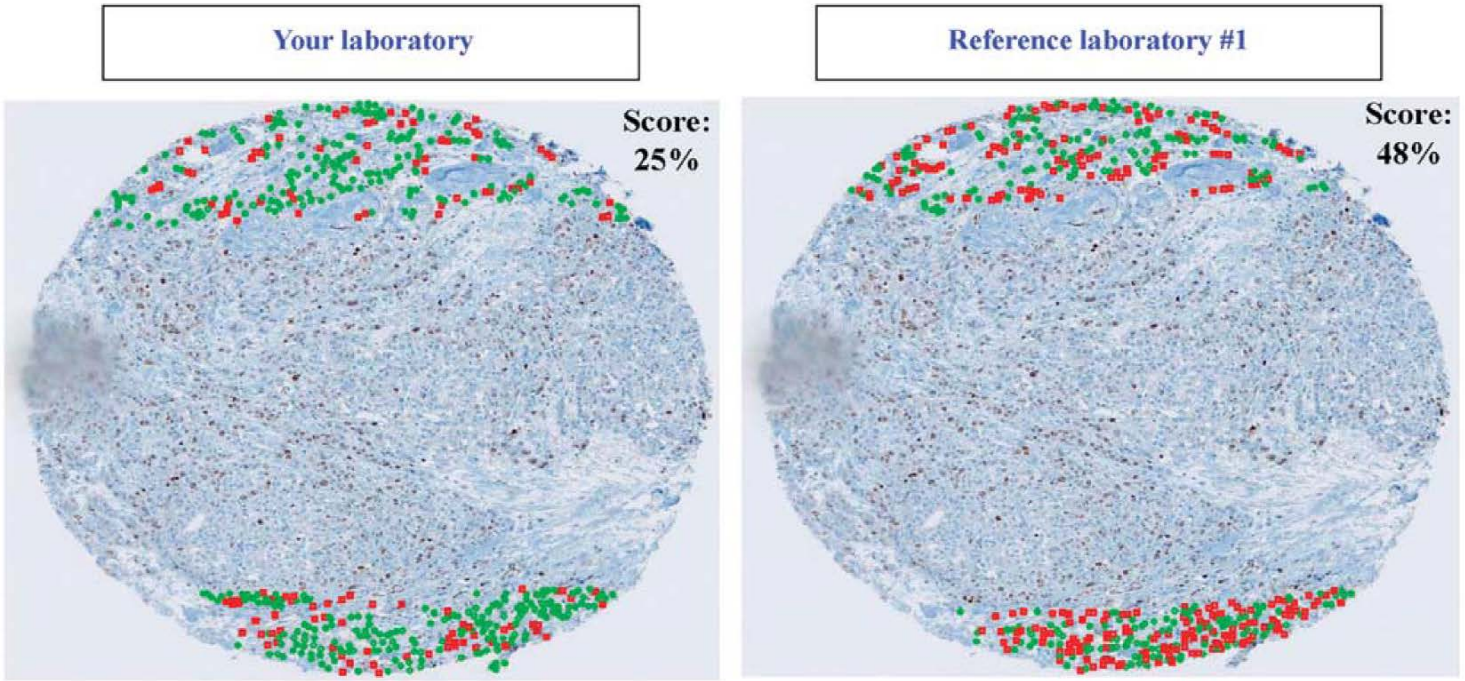
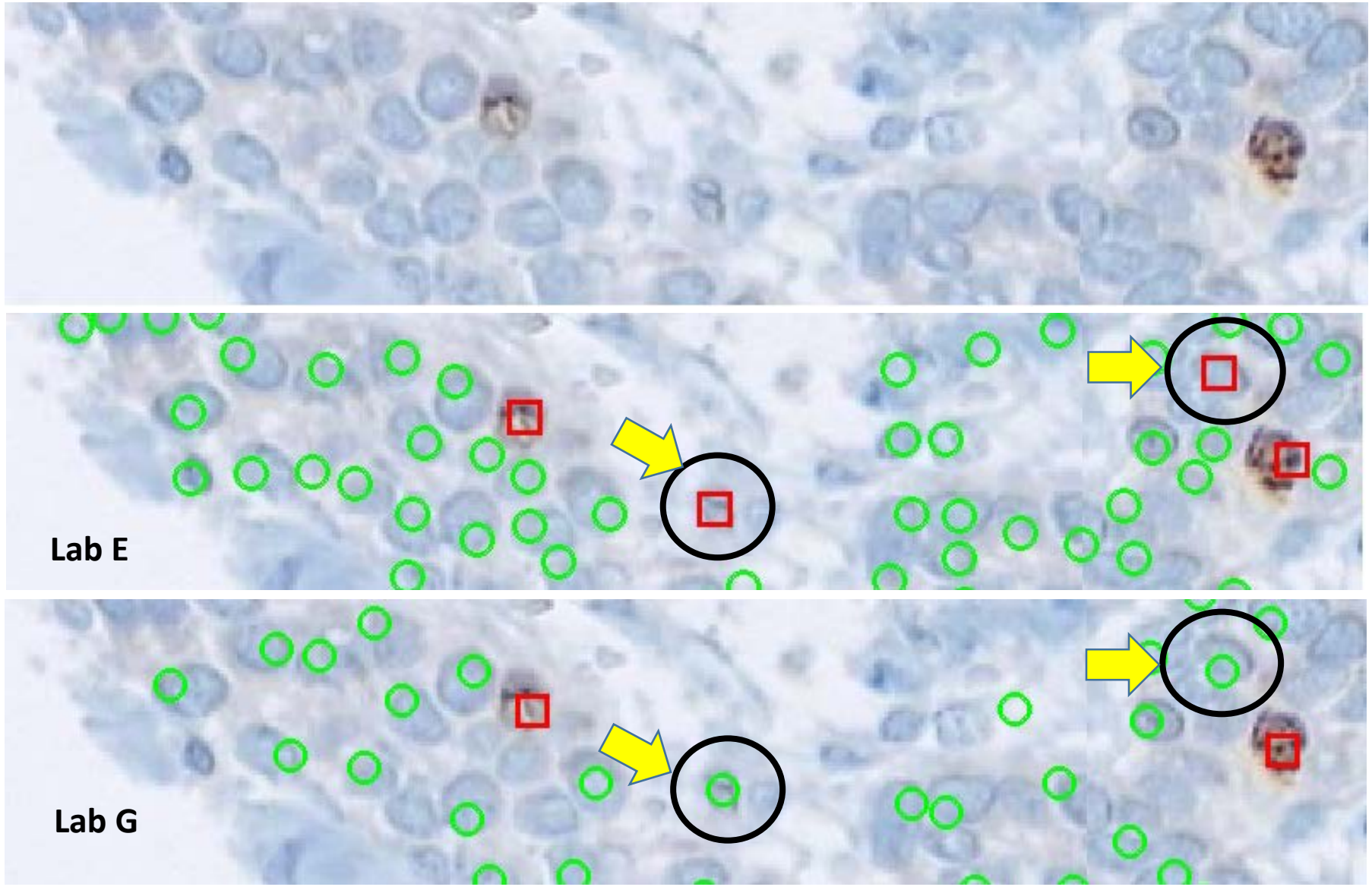



**Figure 1** Example of feedback provided to scorer in the calibration exercise. Red = Scorer assessed nucleus as Ki67 positive. Green = Scorer assessed nucleus as Ki67 negative.

# Ki67- “what is brown”

**Red** = scored as positive **Green** = scored as negative




Nielsen TO et al SABCS 2013

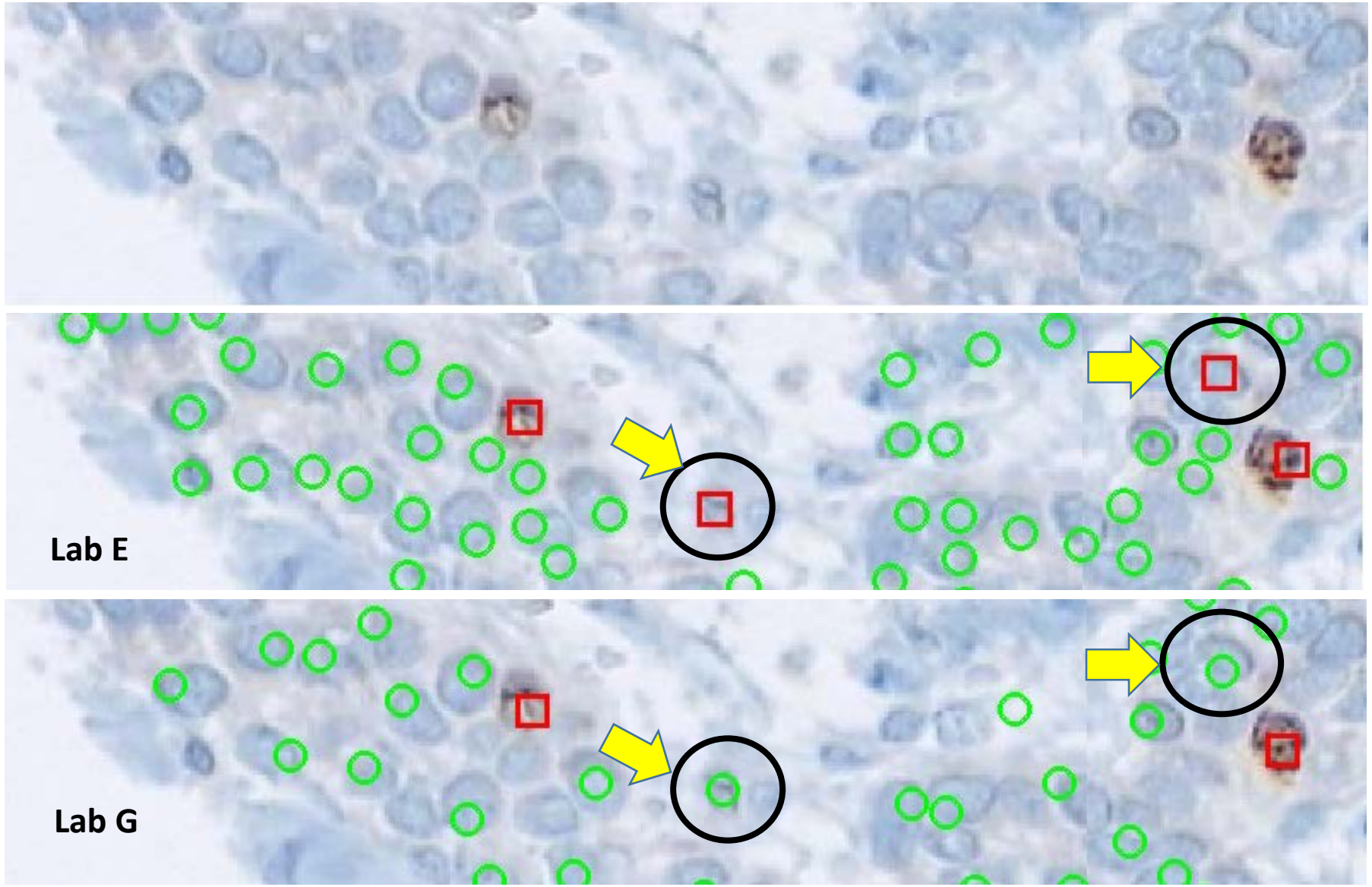
# Consensus - what is brown?

- Never guess!!

- What is not blue is brown!!

# Ki67- “what is brown”

**Red** = scored as positive **Green** = scored as negative




Nielsen TO et al SABCS 2013

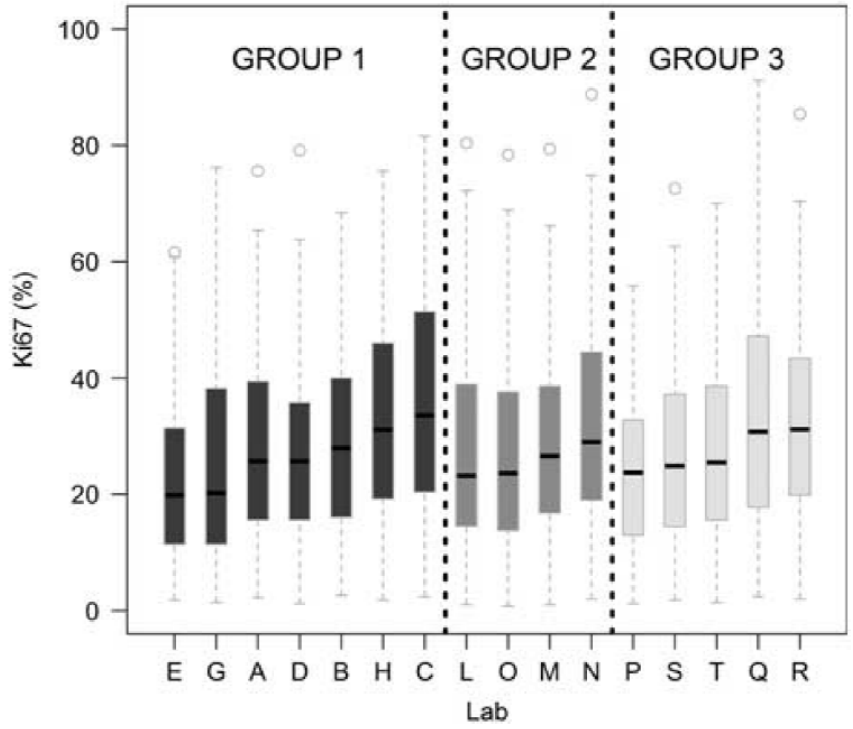



**Figure 2** Ki67 scores (percentage of invasive cancer cells scored positive) of all 16 laboratories scoring on glass, by Group (all laboratories within a Group scored the same tissue microarray section). Laboratories have been ordered according to increasing median Ki67 values within each Group. Each Group represents a given tissue microarray section (boxplot shading: black for Group 1, medium gray for Group 2, and light gray for Group 3). The bottom and top of the box in each box plot represent the first (Q1) and third (Q3) quartiles, and the bold line inside the box represents the median of the distribution. The two bars outside the box represent the lowest datum still within 1.5 × (Q3-Q1) of Q1, and the highest datum still within 1.5 × (Q3-Q1) of Q3 (ie, 1.5 × the inter-quartile range). Any data not within the two bars are outliers and represented with empty circles.

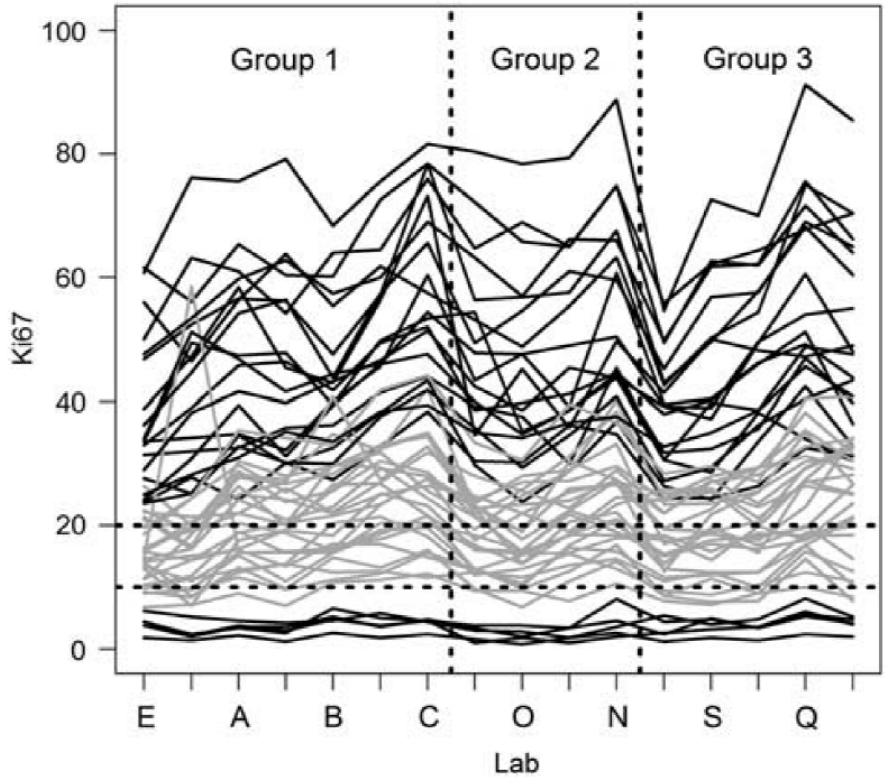



**Figure 3** Variability in Ki67 scores (percentage of invasive cancer cells scored positive) across the 16 laboratories for the 50 cases. Each line represents Ki67 scores for the same case. Lighter-colored lines represent data for the 26 cases for which at least one of the 16 laboratories reported a score in the range $10\% \leq \text{Ki67} \leq 20\%$ (one case per line); the darker lines are the remaining cases. Within each Group, laboratories were looking at the exact same tissue microarray section; between Groups, the laboratories were looking at different sections derived from the same tissue microarray block.

# Ki67 global versus hotspot

- Data to be presented at SABCS 2017

# Case

- Points in favor PA
  - Circumscribed lesion
  - Low mitotic activity
- Points against
  - Irregular margins
  - Some mitotic activity

- Excision was performed
  - Identical morphology and ki67 scores
  - Focally infiltrative margins
  - Inked margins clear

# Clinical issues

- Should the patient get chemotherapy?
- Metaplastic carcinoma – needs chemotherapy
- Pleo Adenoma – no chemotherapy

# Differential Diagnosis

- Pleomorphic adenoma
- Metaplastic carcinoma

**Table 2.** Key features of the breast lesions of uncertain malignant nature

| Entity | Key features |
|---|---|
| Infiltrating epitheliosis (IE) | IE is a rare lesion characterized by infiltrating epithelial islands, solid clusters, ducts and duct-like structures immersed in a scleroelastotic stroma. Proliferating cells feature architectural and cytological patterns and immunohistochemical profile reminiscent of those of usual ductal hyperplasia. The infiltrative nature and the lack of peripheral myoepithelial cells raise the concern that IE is a form of invasive low-grade malignant neoplasm, with some similarities to LG-ASC exist. However, the immunoprofile, benign cytonuclear features, the absence of an *in-situ* carcinoma and focal preservation of peripheral myoepithelial cells support the current view that IE is a form of benign exaggerated hyperplastic process. No events related to a malignant behaviour have been reported in cases diagnosed as IE and the evidence to describe its nature and predict its behaviour compared to benign hyperplastic or low-grade malignant process remains lacking. Therefore the uncertain nature and behaviour of such lesions should be acknowledged |
| Mammary pleomorphic adenoma (PA) | Breast PA is often associated with a papillary lesion similar to other low-grade MBC and adenomyoepithelioma. Despite the perceived indolent benign clinical behaviour of breast PA, local recurrences have been reported in the few published cases and cytologically malignant features characteristic of conventional mammary-type carcinomas have been demonstrated in PA and categorized as 'carcinoma ex pleomorphic adenoma'. In the more common PA in the salivary gland, lymphovascular invasion and distant metastasis have been reported in histologically benign cases. Absence of peripheral myoepithelial cells is a feature of breast PA. These tumours may represent a form of low-grade indolent breast tumour that resides at the lower end of a spectrum of matrix-producing MBC featuring prominent stromal metaplastic differentiation and low-grade cytological features. These tumours are best regarded as PA-like tumours of the breast to reflect the uncertainty of their nature and behaviour |
| Mammary cylindroma | These tumours may represent a variant of low-grade adenoid cystic carcinomas of the breast with prominent cylindromatous differentiation. The behaviour and origin of breast cylindroma may not be the same as the dermal counterparts, and breast tumours show infiltration of the surrounding tissue. Both adenoid cystic carcinoma and breast cylindroma share the same immunoprofile with triple-negative phenotype, p63 and strong c-kit expression. These tumours can be considered as lesions of uncertain malignant nature to reflect the current uncertainty regarding the nature and behaviour of these tumours |
| Microglandular adenosis (MGA) and atypical microglandular adenosis | Despite the infiltrative nature and the lack of peripheral myoepithelial cells around the proliferating glands of MGA, the indolent clinical behaviour in the limited number published in the literature and the bland cytological features render the benign nature of MGA. However, some cases show cytonuclear atypia, associated frequently with ER-negative carcinomas, and the diffuse strong nuclear S100 positivity together with recent molecular evidence suggest that MGA is a neoplastic process. The nature and behaviour of MGA, particularly when associated with atypia, remain unknown, and such uncertainty needs to be acknowledged |

MBC, metaplastic breast carcinoma; ER, oestrogen receptor; LG-ASC, low-grade adenosquamous carcinoma.

Rakha et al Histopathology 2016

# My diagnosis

- Low grade adnexal tumor of salivary/sweat gland type

(pleomorphic adenoma of breast)