Table 1. Proposed guidelines for the assessment of tumor-infiltrating lymphocytes (TILs) in solid tumors: recommendations by an International Immuno-Onoclogy Biomarker Working Group.

1. TILs should be reported separately for the stromal compartment (= % stromal TILs) and the tumor cell compartment (=% intra-tumoral TILs). The reasons are 1) in many tumors the TIL density in both compartments is different, and 2) if the TILs are evaluated simply per tumor area, the density and growth pattern of tumor cells (= a non-immune parameter) will affect the TIL count. The denominator used to determine the % stromal TILs is the area of stromal tissue (i.e. area occupied by mononuclear inflammatory cells over total stromal area), not the number of stromal cells (i.e. fraction of total stromal nuclei that represent mononuclear inflammatory cell nuclei). Similarly, for intra-tumoral TILs the tumor cell area is the denominator. In some tumor types, e.g. breast cancer, it might be decided to evaluate only the stromal TILs.
2. TILs should be evaluated within the borders of the invasive tumor, including both "central tumor" and "invasive margin". These areas may be reported separately when required.
3. The "invasive margin" is defined as a 1mm region centered on the border separating the malignant cell nests from the host tissue. The "central tumor" represents the remaining tumor area.
4. Exclude TILs at a distance outside of the tumor borders. TILs immediately adjacent to the invasive margin, i.e. "peri-tumoral TILs", may be evaluated when required.
5. Exclude TILs in tumor zones with crush artifacts, necrosis and regressive hyalinization, as well as in previous biopsy sites.
6. All mononuclear cells (including lymphocytes and plasma cells) should be scored, but polymorphonuclear leukocytes (neutrophils) should be excluded.
7. One section (4-5 μm, magnification 200-400x) per patient can be considered to be sufficient for practical purposes. However, assessing additional sections for each case whenever possible and reporting the number of sections reviewed per case specifically in the manuscript is recommended since the extent of heterogeneity for different tumor types is unknown.
8. Full sections are preferred over biopsies whenever possible. Cores can be used in the pre-therapeutic neoadjuvant setting; currently no validated methodology has been developed to score TILs after neo-adjuvant treatment.
9. A full assessment of average TILs in the tumor area (central tumor and invasive margin) should be used. Do not focus on hotspots.
10. TILs should be assessed as a continuous variable, as this may provide more biologically relevant information and allow more accurate statistical analyses. However, in daily practice most pathologists will report discrete estimates, for example 13.5% will be rounded to 15%. Pathologists should report their scores in as

much detail as the pathologist feels comfortable with.
11. For assessment of percentage values, the dissociated growth pattern of lymphocytes needs to be taken into account. The percentage of stromal TILs is a semi-quantitative parameter for this assessment, for example, 80% stromal TILs means that 80% of the stromal area shows a dense mononuclear infiltrate. Lymphocytes typically do not form solid cellular aggregates, therefore the designation “100% stromal TILs” would still allow some empty tissue space between the individual lymphocytes.
12. No formal recommendation for a clinically relevant TIL threshold(s) can be given at this stage. A valid methodology is currently more important than issues of thresholds for clinical use, which will be determined once a solid methodology is in place.

Table 2. Additional points for attention when assessing TILs in different tumor types.

Invasive breast carcinoma
- Refer to Salgado et al [14]. Consensus guidelines are reproduced in Table 3.
Ductal carcinoma in situ and other pre-malignant lesions
- Refer to Pruneri et al 2016, supplementary table 1 [77]. - Stromal area is defined as the specialized stroma surrounding the ducts involved by in-situ carcinoma, or when this is not clear, an area surrounding the ducts within 2 high power fields (approximately 1mm). - Any type of circumferential infiltrate should be taken into account, including minimal, partial, subtotal and total circumferential TILs. - Exclude TILs that are in continuity between the invasive tumor and the in-situ lesions with no clear distinction as to whether these are TILs associated with the invasive or in situ component.
Melanoma
- Currently only iTILs are scored in the clinical setting. sTILs and/or peri-tumoral TILs may be reported separately in research settings. - Only the vertical growth phase of the primary tumor is evaluated. - Further research may determine what %iTILs corresponds to the traditional categorization of brisk/non-brisk/absent.
Colorectal carcinoma
- Separately reporting invasive margin and central tumor TILs is recommended. Invasive margin TILs appear to have the most prognostic significance in this setting.
Upper gastrointestinal tract carcinomas
- Early evidence supports evaluating only sTILs in gastric carcinoma, due to a lack of prognostic significance of iTILs. This finding requires further validation. - There is insufficient data on pancreatic ductal adenocarcinoma and hepatocellular carcinoma to make specific recommendations.
Non-small cell lung carcinoma
- sTILs and iTILs should be separately reported in the research setting at present. Insufficient evidence is available to support evaluating only sTILs over a combined assessment. - Do not include areas with pure intra-alveolar tumor spread (aerogenic spread) or with pure lepidic growth (no desmoplastic reaction). - Do not include alveolar macrophages.
Ovarian carcinoma
- Both the central tumor and invasive margin should be included, but it is not currently recommended to report these regions separately. - iTILs and sTILs should be separately reported at present, as both compartments appear to have prognostic relevance. Further research may

determine the relative importance of the different compartments. - Include TILs in the stroma pertaining to fibrovascular cores of papillary structures. - Include the invasive margin of superficial peritoneal or ovarian deposits.
Head and neck squamous cell carcinoma
- Care should be taken to exclude pre-existing lymphoid stroma from the assessment in oropharyngeal (i. e. tonsillar and base of tongue) tumors. If a desmoplastic stroma is present, sTILs can be scored in this reactive stroma (as for lymph node metastases).
Genitourinary carcinomas
- Separate reporting of iTILs and sTILs is recommended – this is important in the context of immune checkpoint inhibitor therapy with atezolizumab in urothelial carcinoma, where the PD-L1 "immune cell" score is derived from the sTILs score. - Care should be taken to avoid areas of diathermy/coagulation artifact, a common finding in bladder tumor specimens. - Non-invasive papillary structures are not currently included in the assessment. - There is insufficient data on prostate carcinoma and renal cell carcinoma to make specific recommendations.
Primary brain tumors
- No evidence based recommendations on the optimal method for TIL quantification can be made at present. - Immunohistochemistry may be required to clearly identify TILs and distinguish immune cells from pre-existing or neoplastic glial and neuronal cells. - Consideration should be given to separately reporting TILs in the central tumor, perivascular areas, perinecrotic areas and the invasive margin.
Metastatic tumor deposits
- In metastatic deposits within lymph nodes, if a desmoplastic stroma is present, sTILs and iTILs can be scored as for the primary lesion. If a desmoplastic stroma is not present, focus only on iTILs. Exclude the pre-existing lymphoid stroma. - Other sites are evaluated as for the primary lesion. - Future research should focus on the relative clinical utility of evaluating TILs in the primary tumor or in the most recent tumor tissue available.

Table 3. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014.
Reproduced from Salgado et al [14] with permission from Oxford University Press on behalf of the European Society for Medical Oncology.

1. TILs should be reported for the stromal compartment (=% stromal TILs). The denominator used to determine the % stromal TILs is the area of stromal tissue (i.e. area occupied by mononuclear inflammatory cells over total intra-tumoral stromal area), not the number of stromal cells (i.e. fraction of total stromal nuclei that represent mononuclear inflammatory cell nuclei).
2. TILs should be evaluated within the borders of the invasive tumor.
3. Exclude TILs outside of the tumor border and around DCIS and normal lobules.
4. Exclude TILs in tumor zones with crush artifacts, necrosis, regressive hyalinization as well as in the previous core biopsy site.
5. All mononuclear cells (including lymphocytes and plasma cells) should be scored, but polymorphonuclear leukocytes are excluded.
6. One section (4–5 μm, magnification ×200–400) per patient is currently considered to be sufficient.
7. Full sections are preferred over biopsies whenever possible. Cores can be used in the pretherapeutic neoadjuvant setting; currently no validated methodology has been developed to score TILs after neoadjuvant treatment.
8. A full assessment of average TILs in the tumor area by the pathologist should be used. Do not focus on hotspots.
9. The working group's consensus is that TILs may provide more biological relevant information when scored as a continuous variable, since this will allow more accurate statistical analyses, which can later be categorized around different thresholds. However, in daily practice, most pathologists will rarely report for example 13.5% and will round up to the nearest 5%–10%, in this example thus 15%. Pathologist should report their scores in as much detail as the pathologist feels comfortable with.
10. TILs should be assessed as a continuous parameter. The percentage of stromal TILs is a semi-quantitative parameter for this assessment, for example, 80% stromal TILs means that 80% of the stromal area shows a dense mononuclear infiltrate. For assessment of percentage values, the dissociated growth pattern of lymphocytes needs to be taken into account. Lymphocytes typically do not form solid cellular aggregates; therefore, the designation '100% stromal TILs' would still allow some empty tissue space between the individual lymphocytes.
11. No formal recommendation for a clinically relevant TIL threshold(s) can be given at this stage. The consensus was that a valid methodology is currently more important than issues of thresholds for clinical use, which will be determined once a solid

methodology is in place. Lymphocyte predominant breast cancer can be used as a descriptive term for tumors that contain ‘more lymphocytes than tumor cells’. However, the thresholds vary between 50% and 60% stromal lymphocytes.