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## Supplementary information

# The single-cell pathology landscape of breast cancer

In the format provided by the authors and unedited

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**SI Guide**

The SI file contains example images from the analyzed cohort and Supplementary Tables 1-9. The Supplementary Tables yield an overview over the clinical and patient information and summarize the output of statistical analyses.

**Supplementary Images:**

Supplementary Images 1: Summary example images from different patients of the analyzed cohort; (**top**) 6-color image of representative markers, (**bottom**) same image with single-cells colored by cell type metacluster overlaid with an example (**a**) epithelial or (**b**) microenvironment community type contained frequently in the respective image. Each marker was individually scaled to enable visualization. Scale bar = 100 µm.

Supplementary Images 2: Example images from different patients of the analyzed cohort, each highlighting an individual epithelial or microenvironment community type. Scale bar = 100 µm.

Supplementary Images 3: Example images representing a tumor from each SCP subgroup. (**left**) 6-color image of representative markers, (**right**) same image with single-cells colored by cell type metacluster. Scale bar = 100 µm.

**Supplementary Information Tables:**

Supplementary Table 1: Overview of patient clinical metadata for cohort from University Hospital Basel including tumor grade; TNM score (tumor size and invasion, lymph nodal involvement, distant metastasis); overall and disease-free survival; immunohistochemistry classification of ER, PR, and HER2 receptors; and clinical subgroup.

Supplementary Table 2: Antibody conjugates used in staining panel.

Supplementary Table 3: Summary of clinical parameters for each single-cell pathology subgroup.

Supplementary Table 4: (**a-c**) Coxph and (**d-f**) logrank tests for differences in overall survival between each single-cell pathology subgroup and the rest of the patients (**a, d**) in the cohort, (**b, e**) in similar SCP subgroups, and (**c, f**) in the patients clinically categorized as $HR^+/HER2^-$.

Supplementary Table 5: (**a**) Coxph and (**b**) logrank tests for differences between disease-free survival of each single-cell pathology subgroup and the rest of the patients in the cohort.

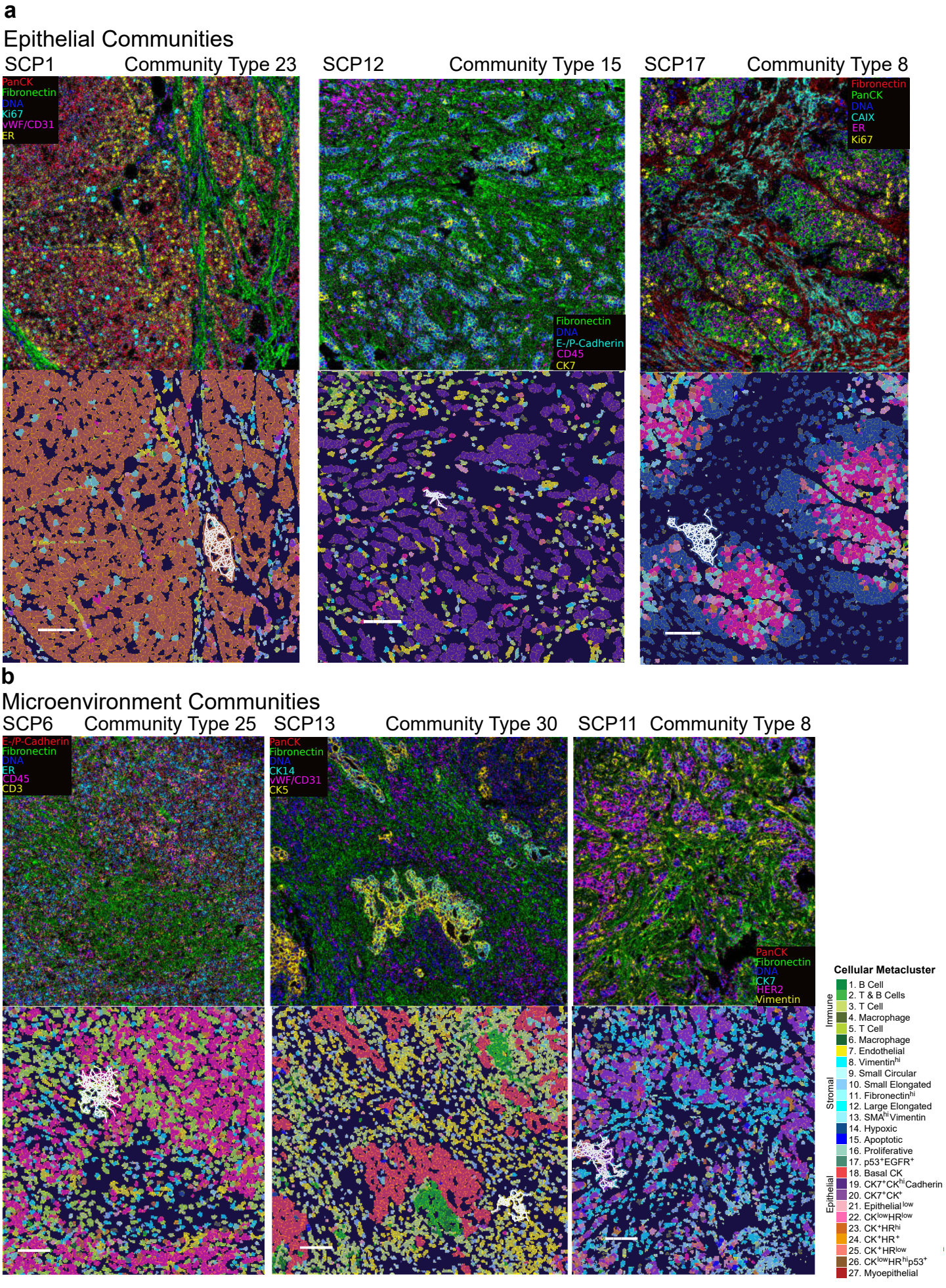
Supplementary Table 6: (**a**) Coxph and (**b**) logrank tests for differences between overall survival of stromal environment subgroup and the rest of the patients in the cohort.

Supplementary Table 7: (**a**) Coxph and (**b**) logrank tests of differences between disease-free survival of stromal environment subgroup and the rest of the patients in the cohort.

Supplementary Table 8: Likelihood ratio tests between nested coxph models. The null hypothesis is that the larger model (more variables) is not better than the smaller one. P values < 0.05 reject the null hypothesis.

Supplementary Table 9: Overview of patient clinical metadata for cohort from University Hospital Zurich.

# Supplementary Images 1




Supplementary Images 1: Summary example images from different patients of the analyzed cohort; (top) 6-color image of representative markers, (bottom) same image with single-cells colored by cell type metacluster overlaid with an example (a) epithelial or (b) microenvironment community type contained frequently in the respective image. Each marker was individually scaled to enable visualization. Scale bar = 100 µm.

# Supplementary Images 2

## Epithelial Community Examples

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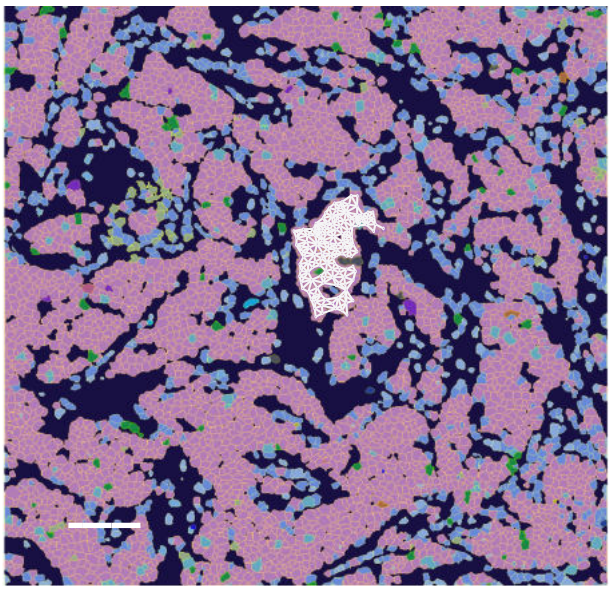

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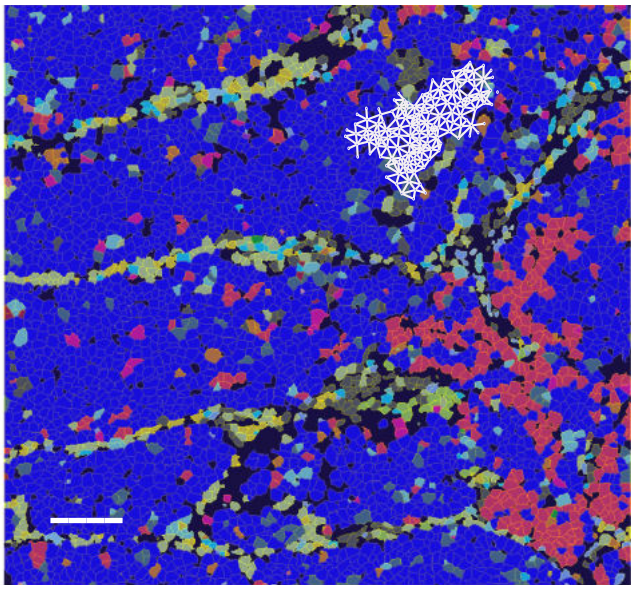

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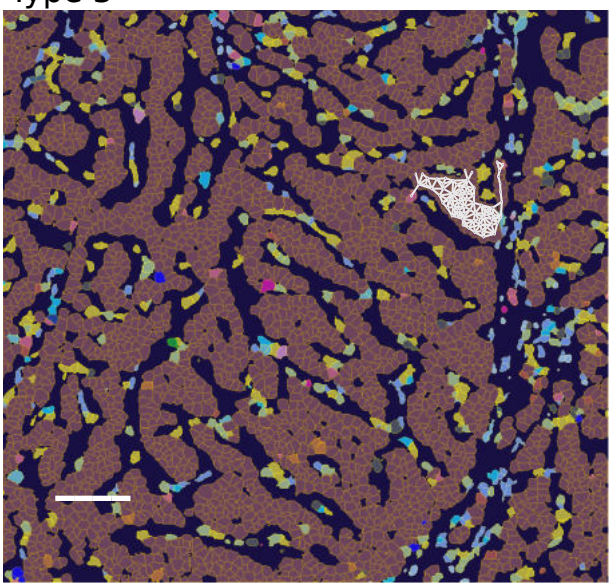

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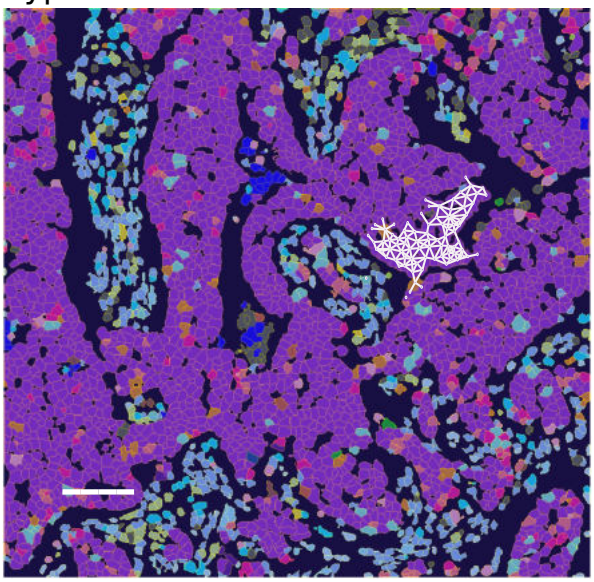

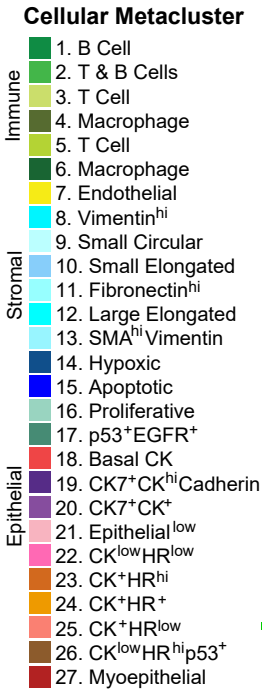


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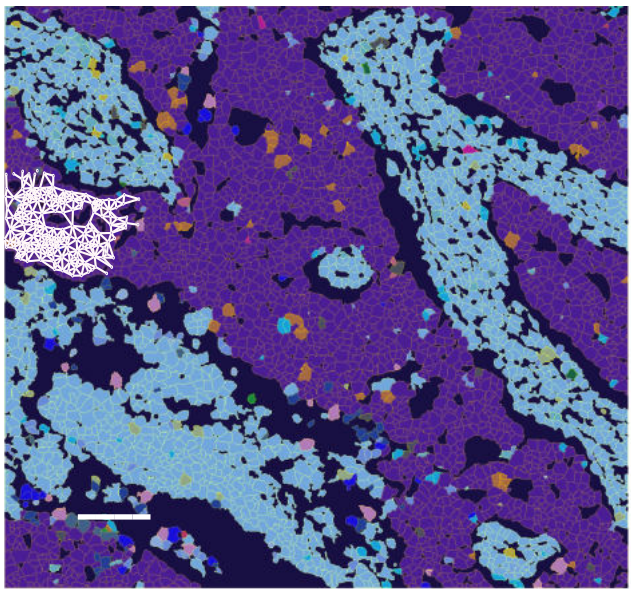

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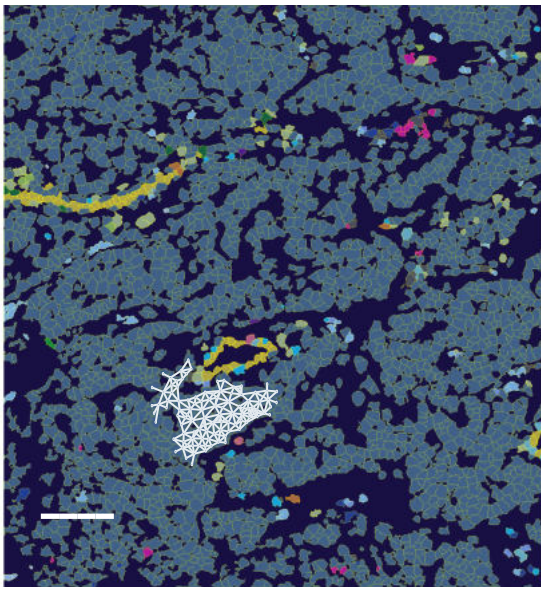

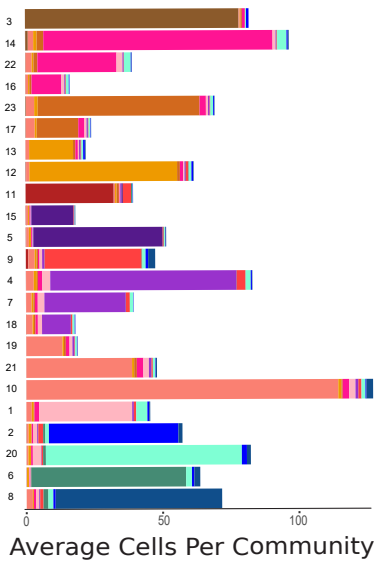

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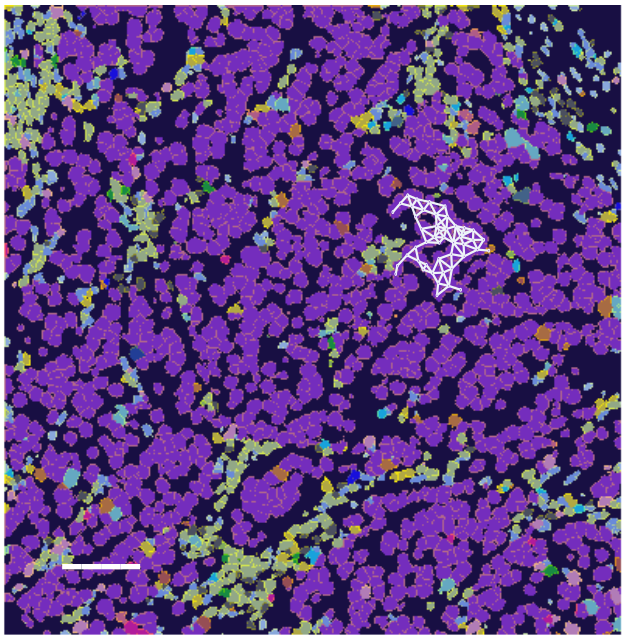

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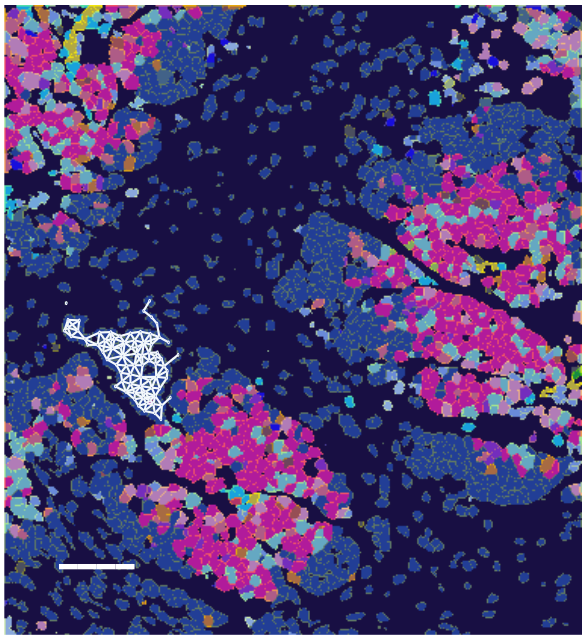

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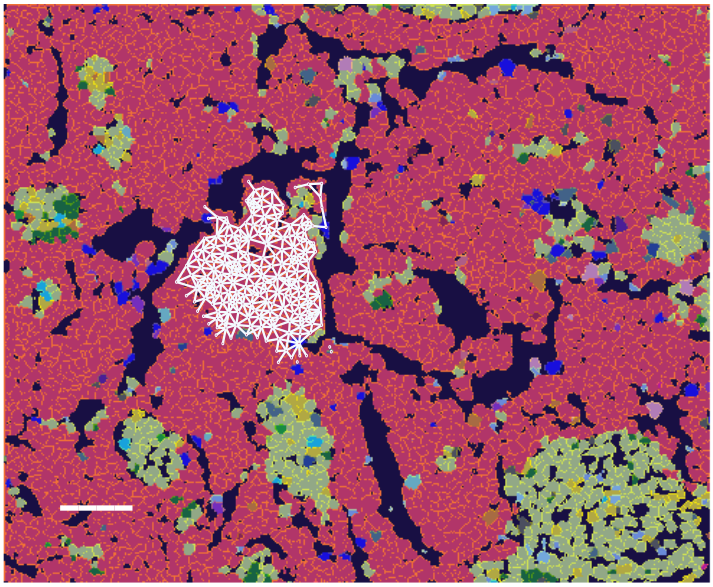

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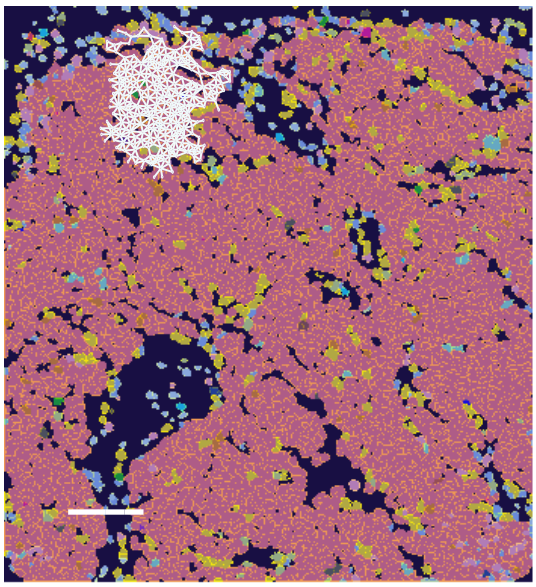

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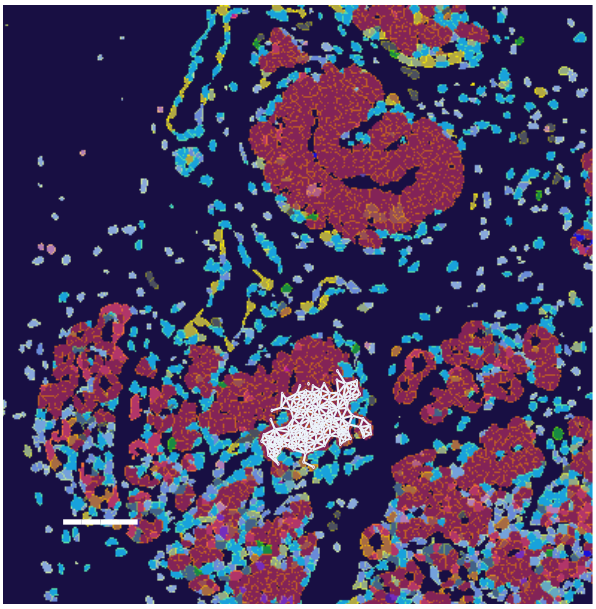

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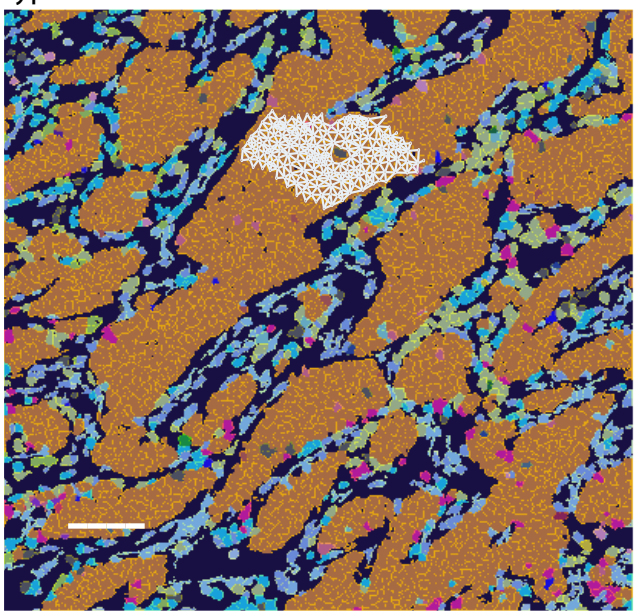

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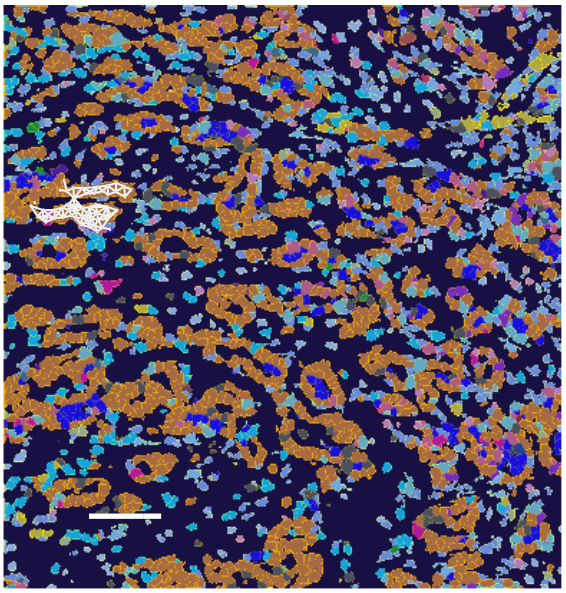

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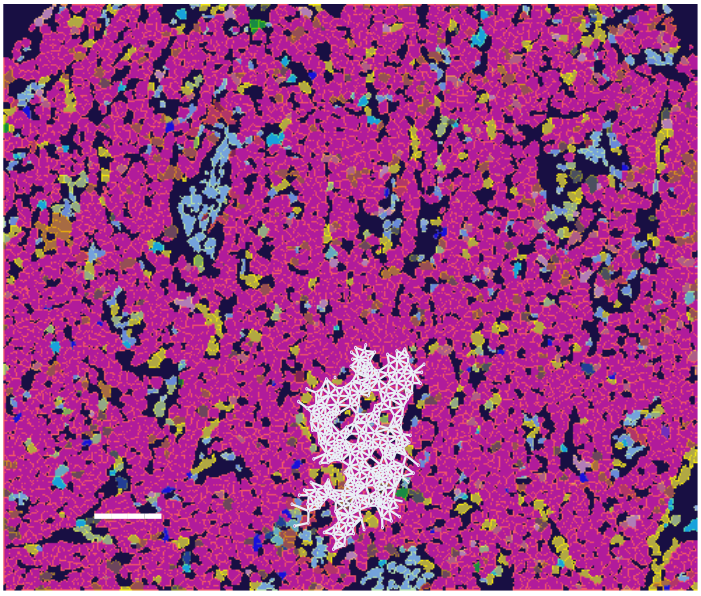

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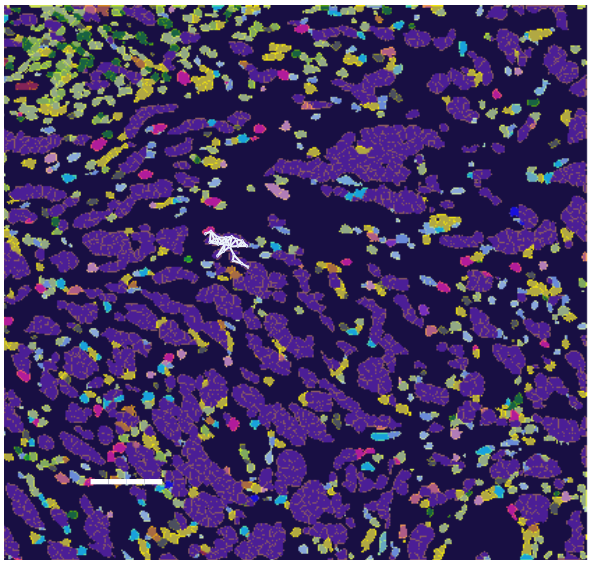

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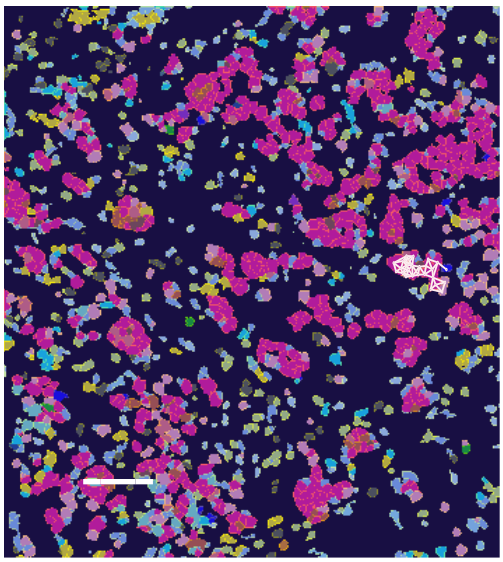

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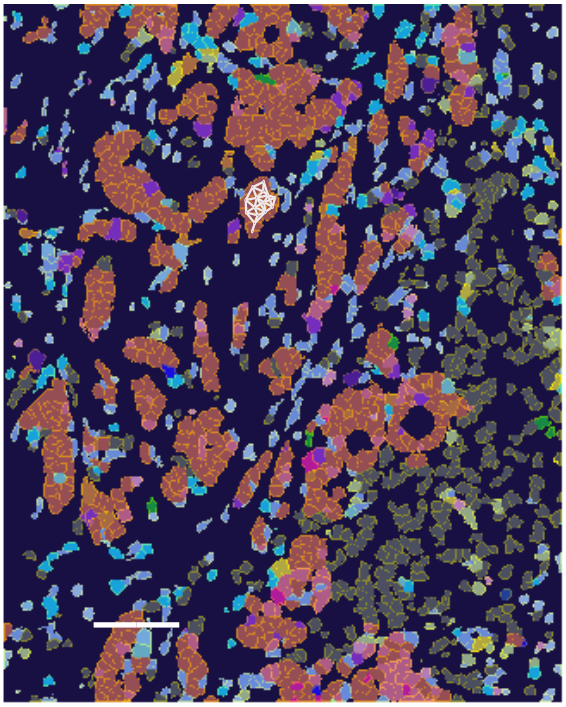

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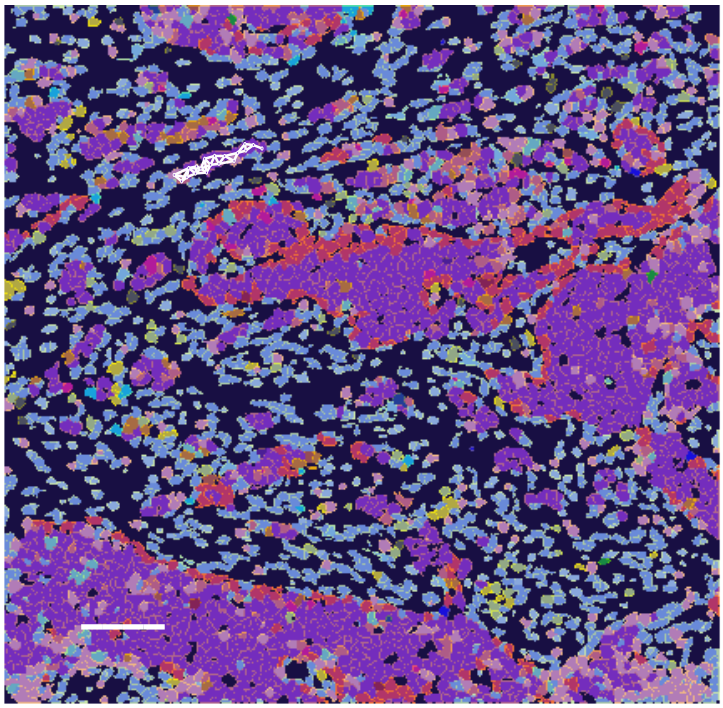

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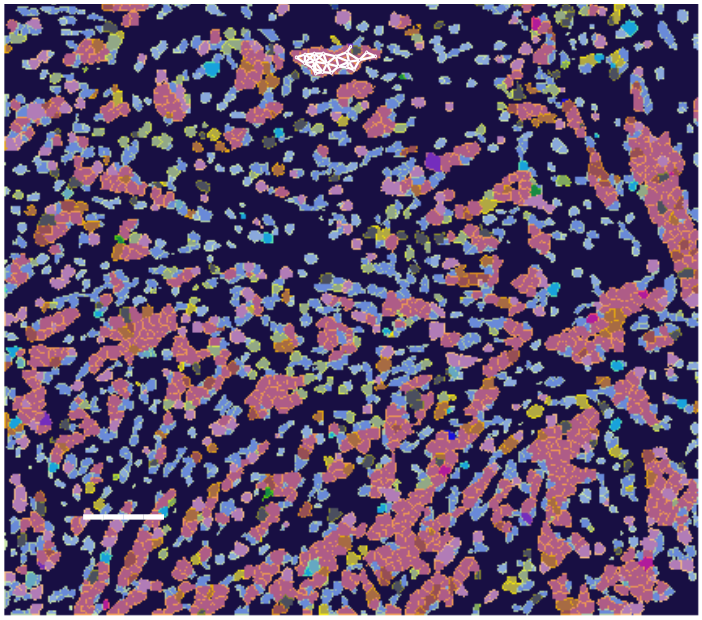

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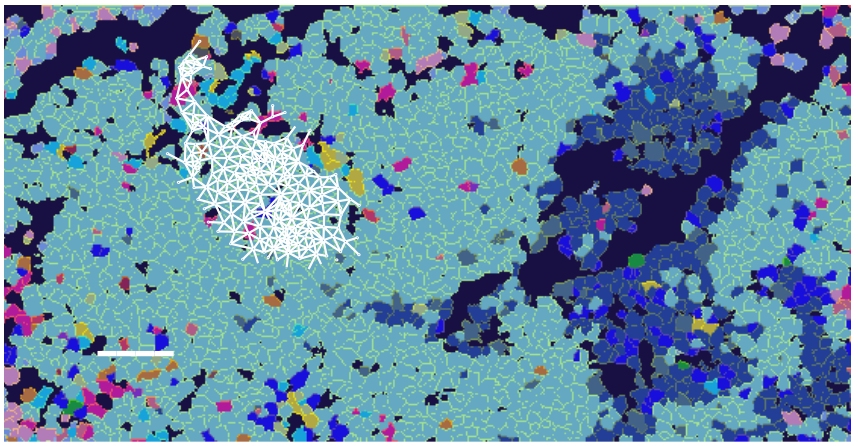

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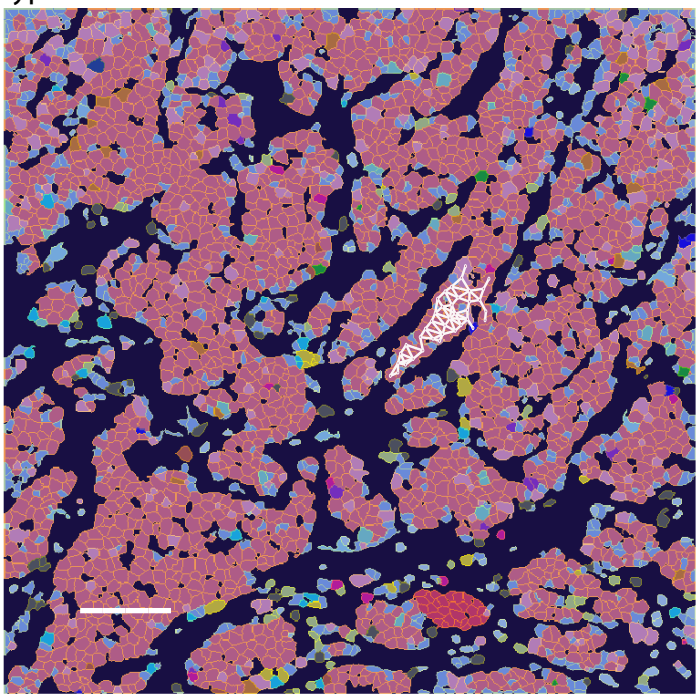

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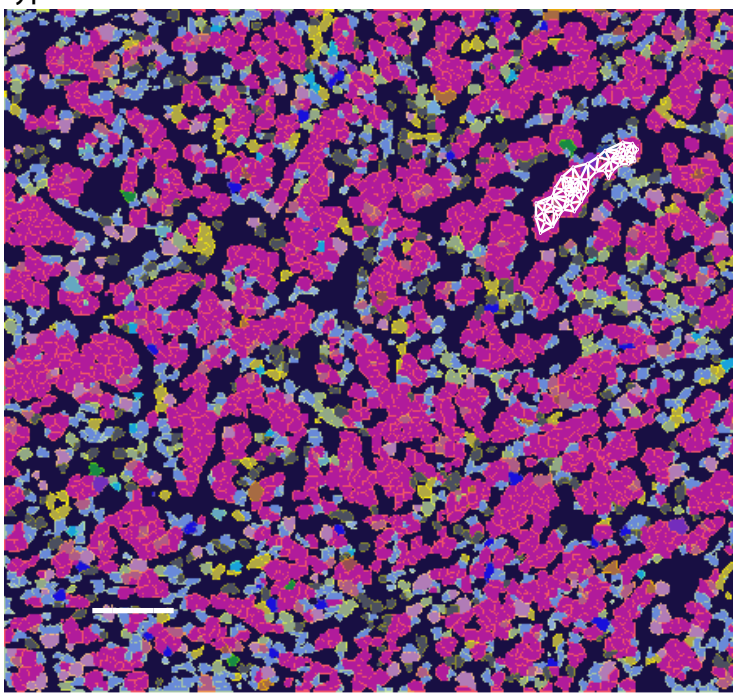

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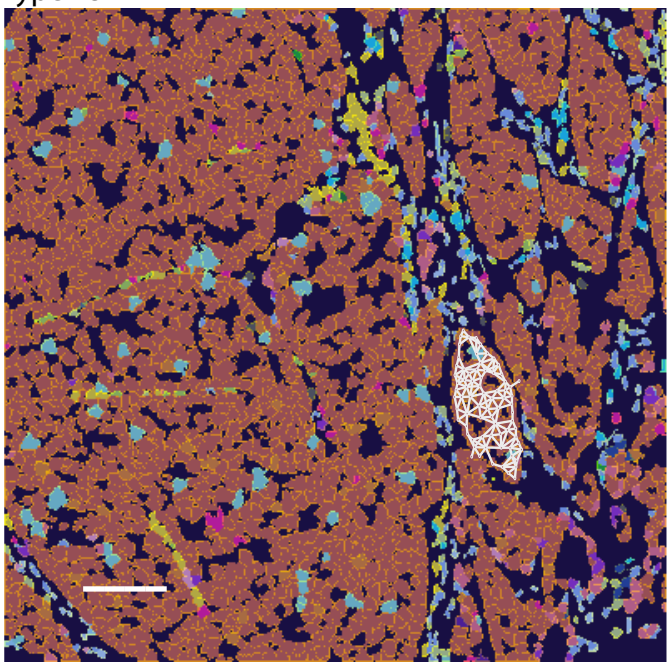

# Microenvironment Community Examples

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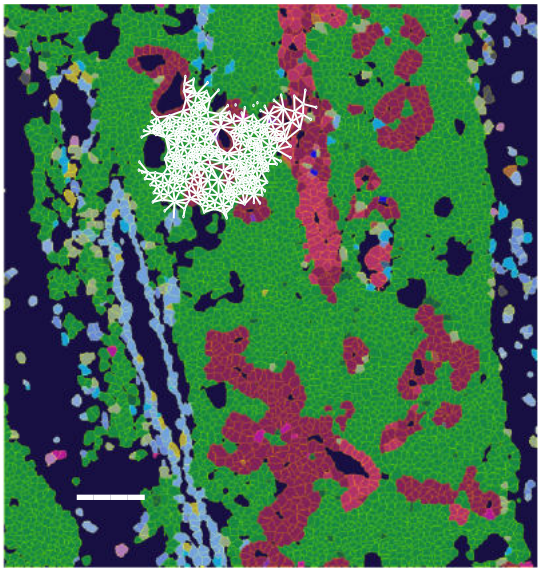

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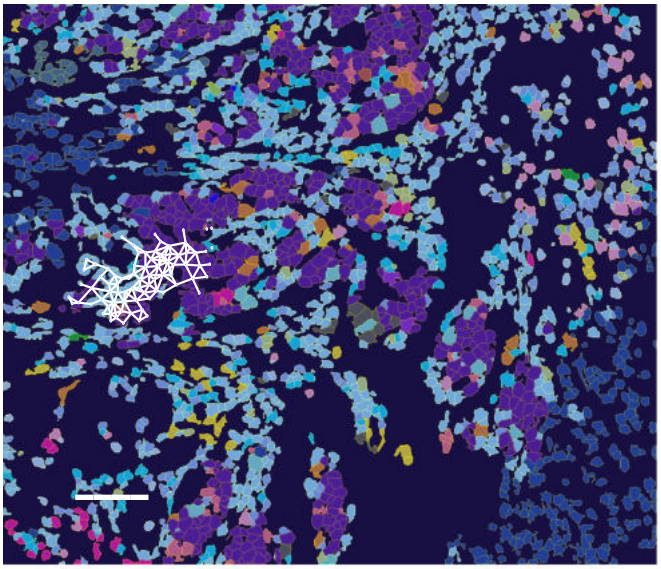

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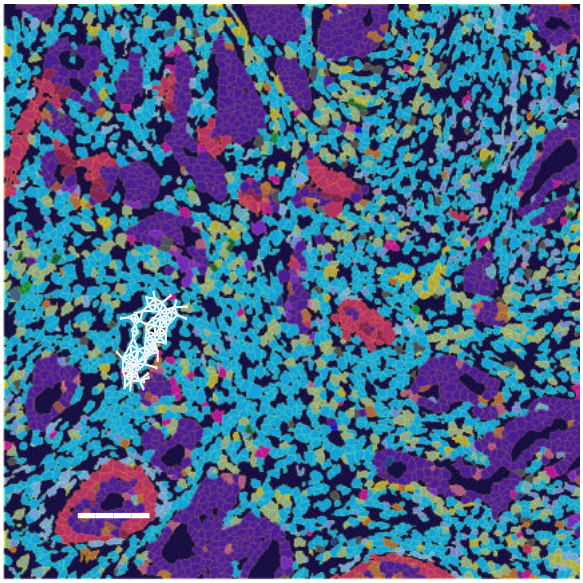

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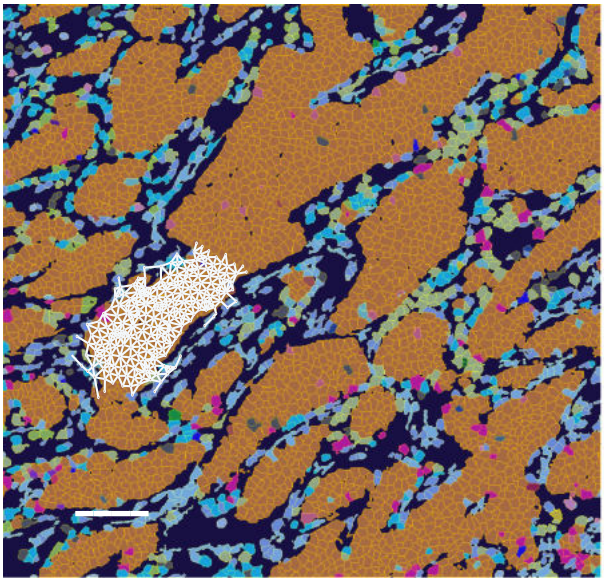

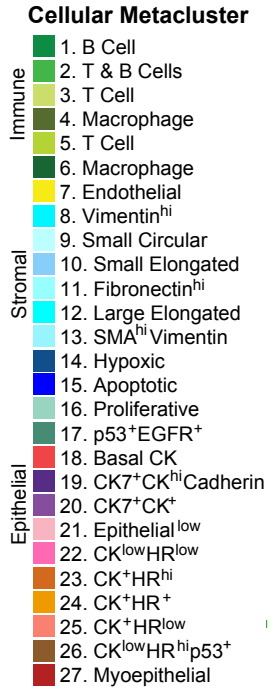


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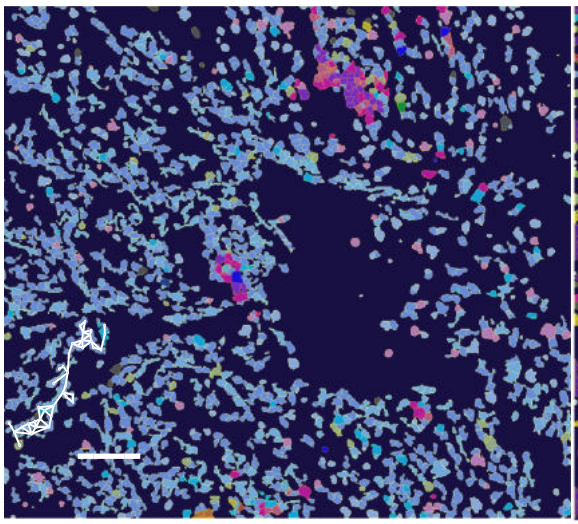

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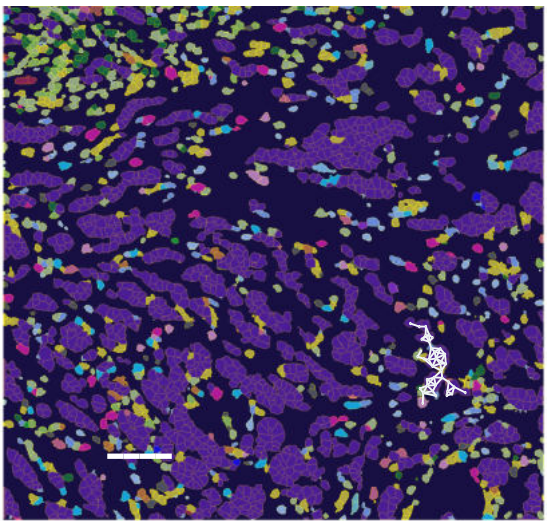

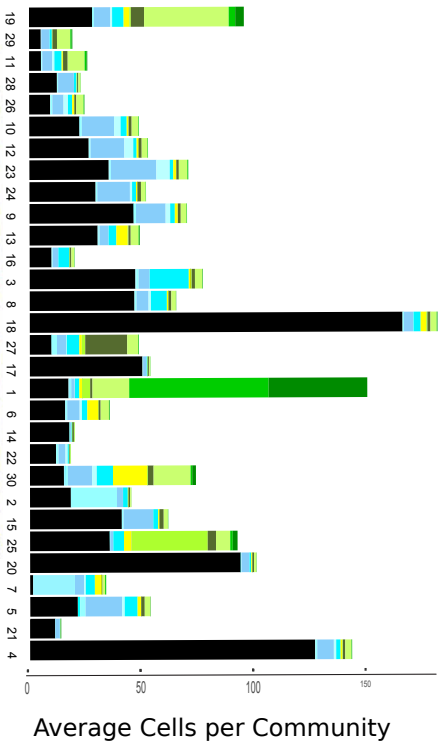

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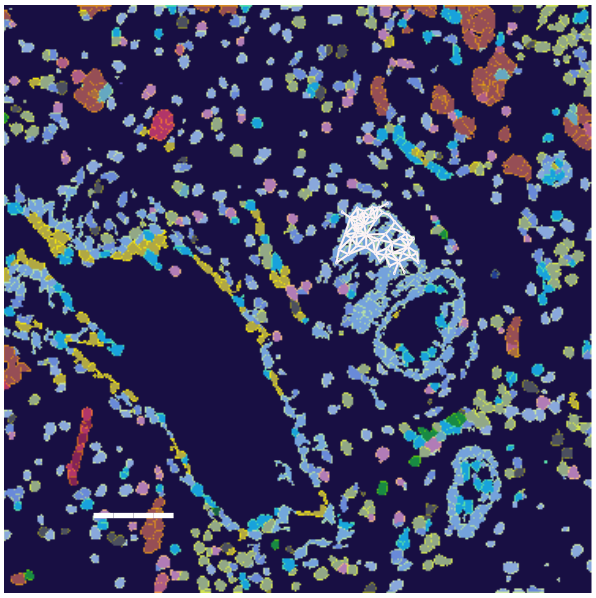

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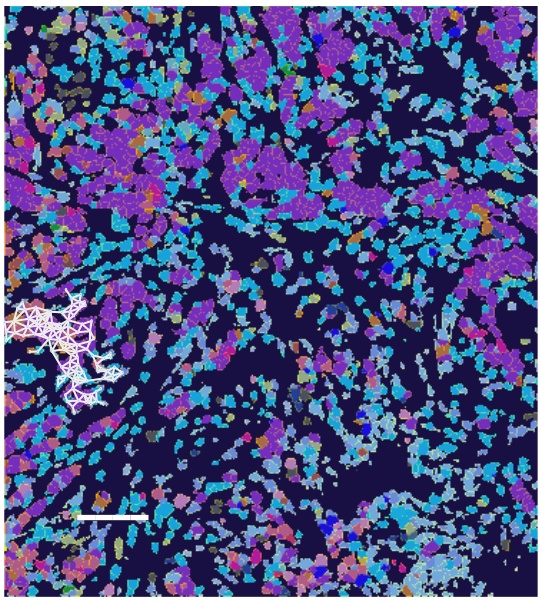

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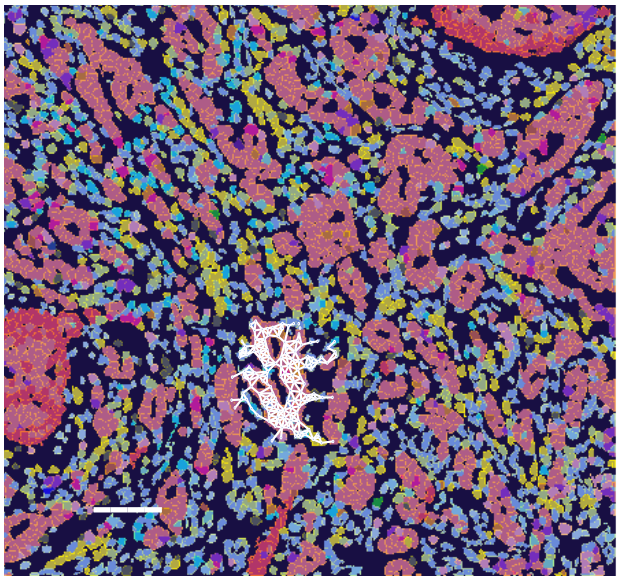

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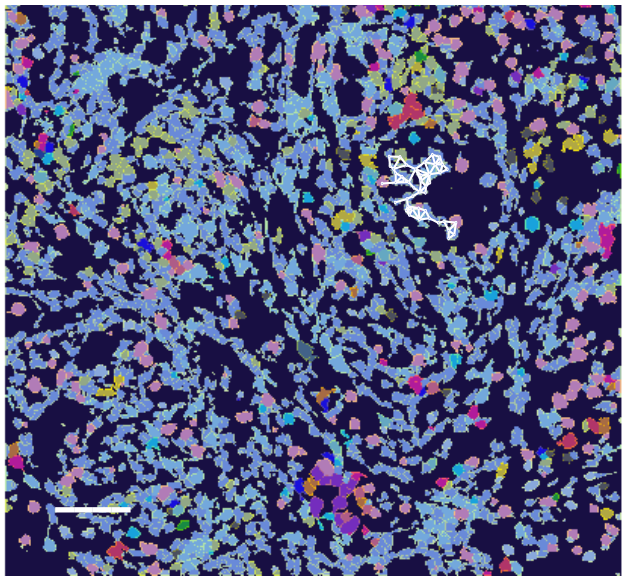

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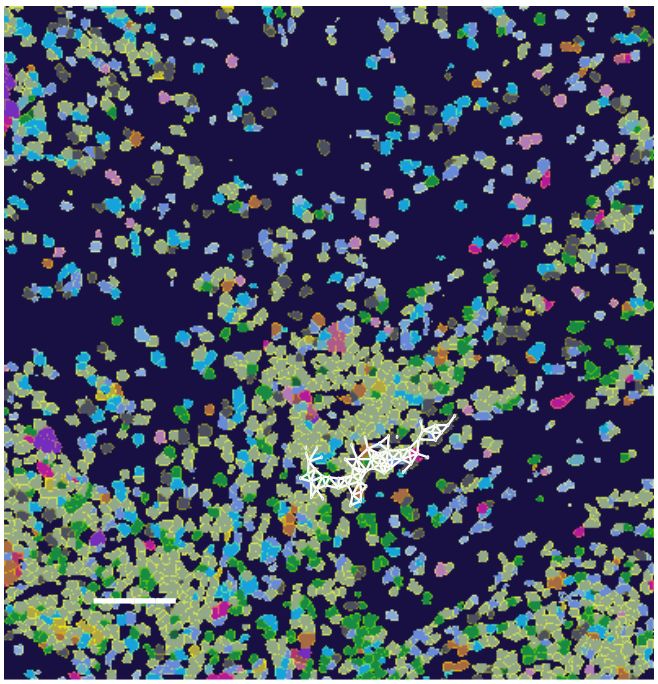

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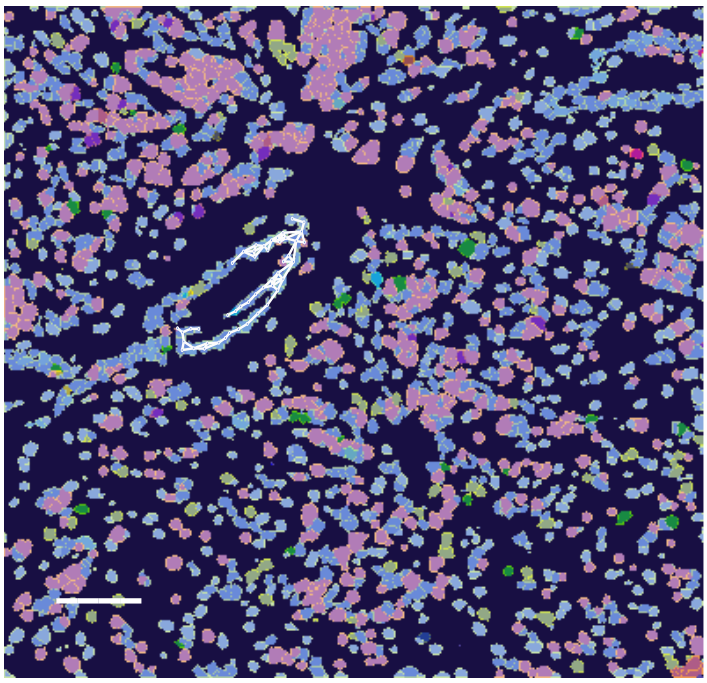

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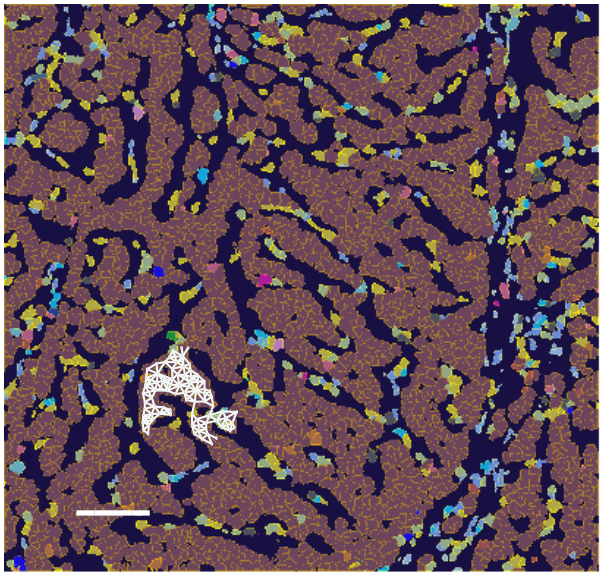

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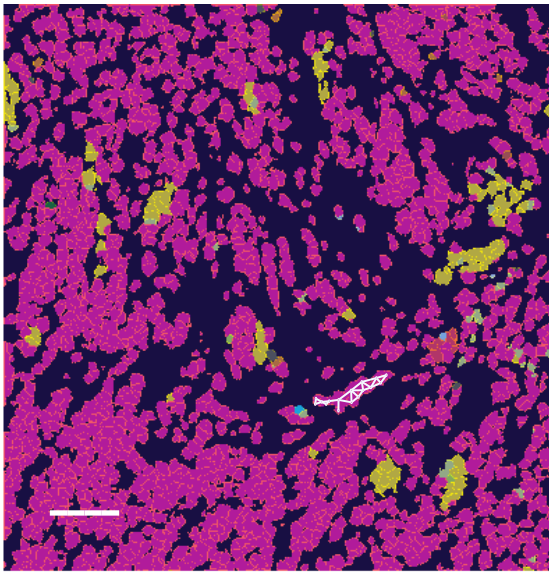

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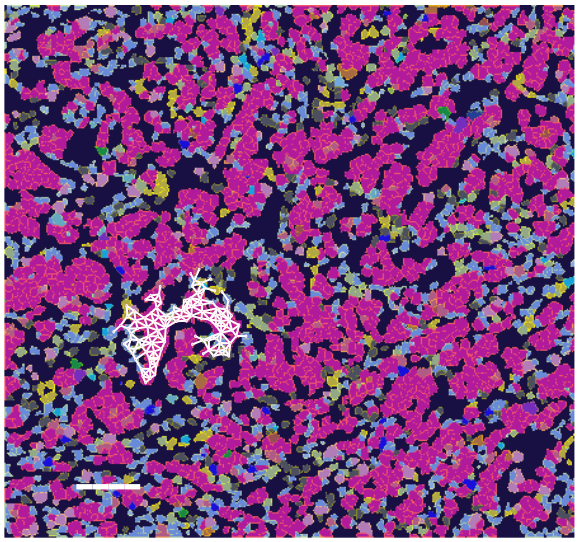

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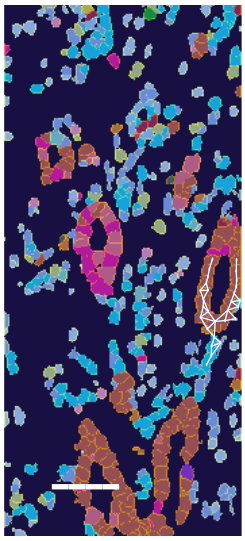

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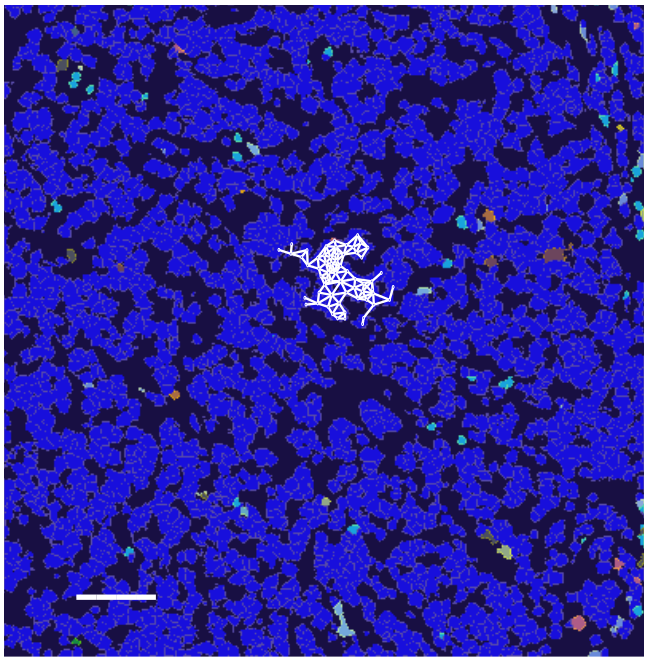

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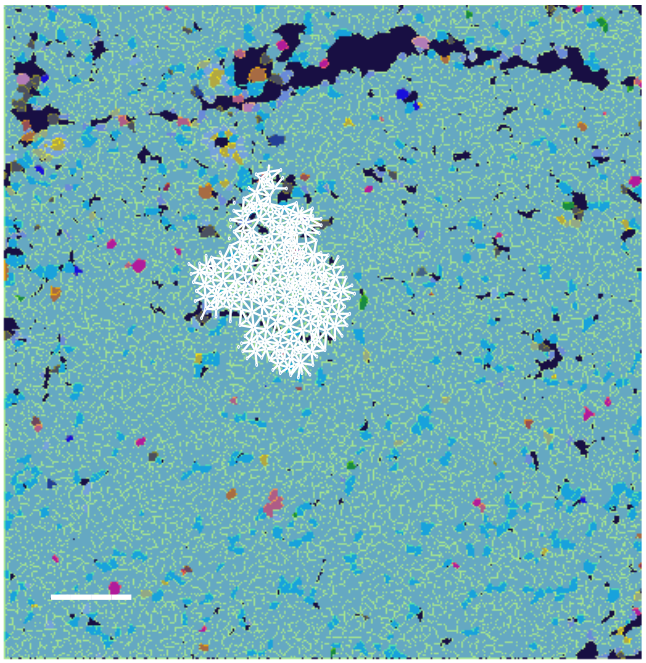

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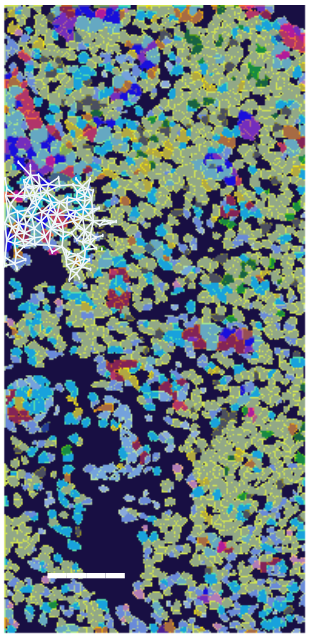

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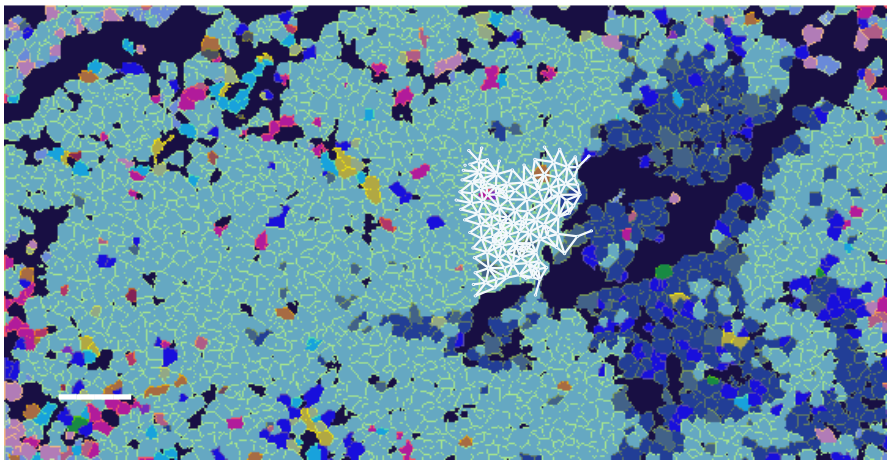

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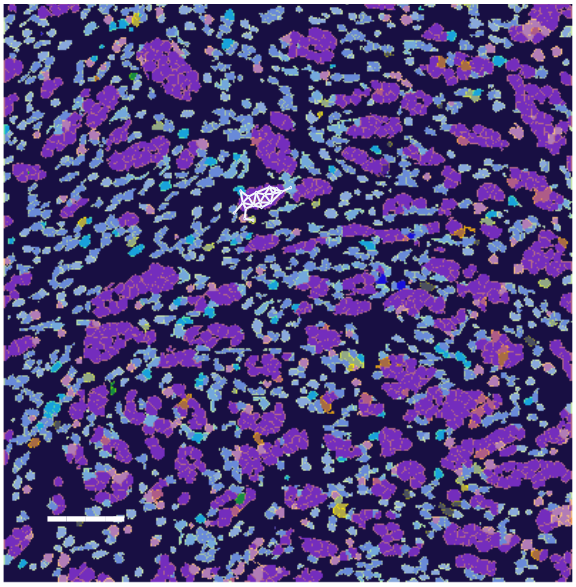

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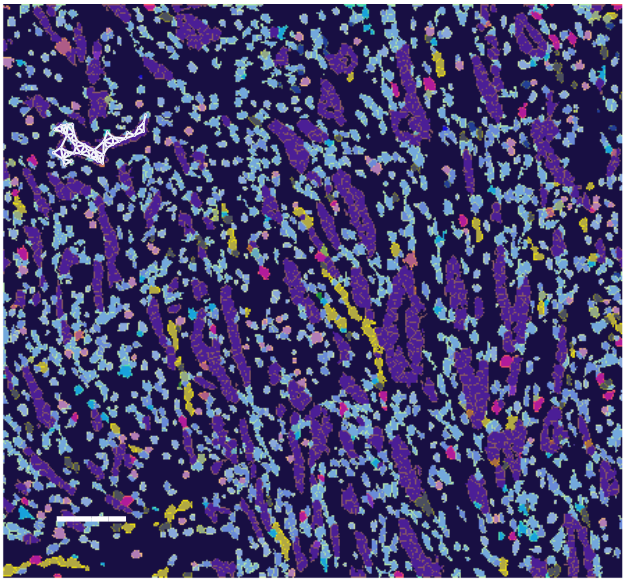
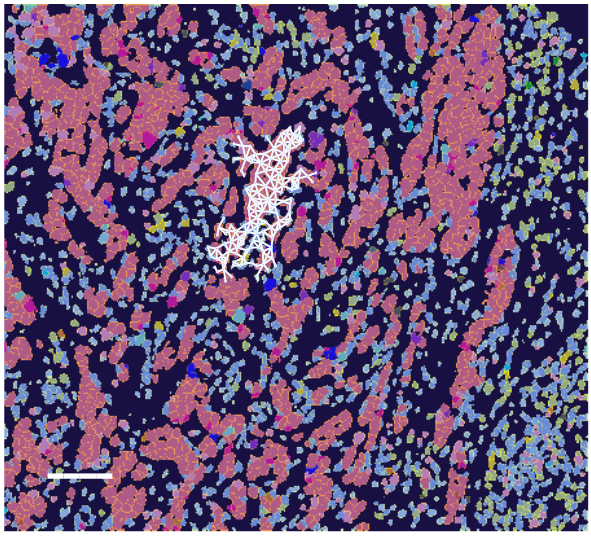
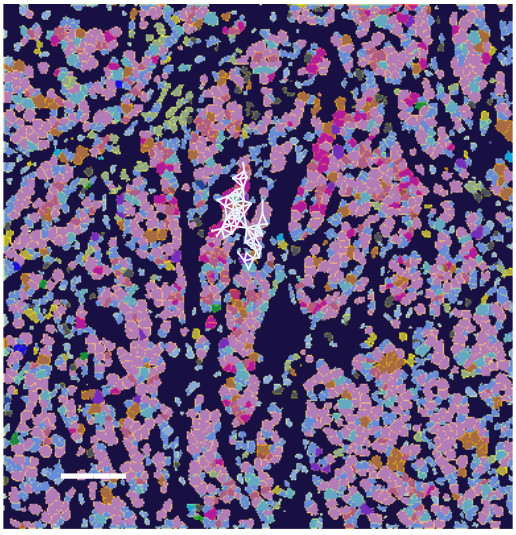


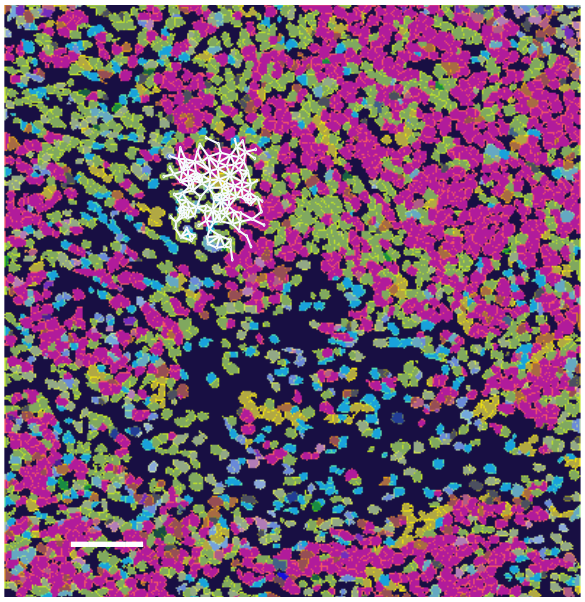
Type 23



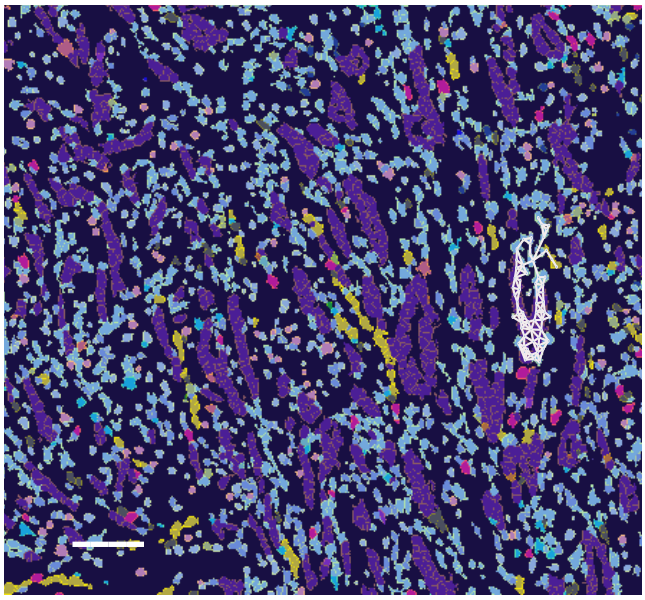
Type 24



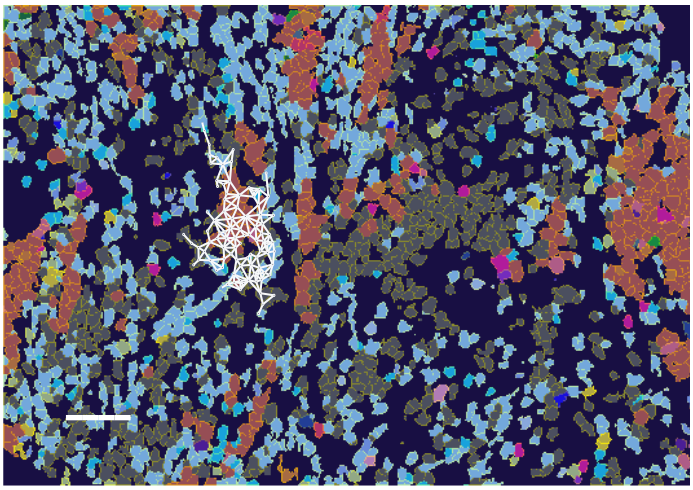
Type 25



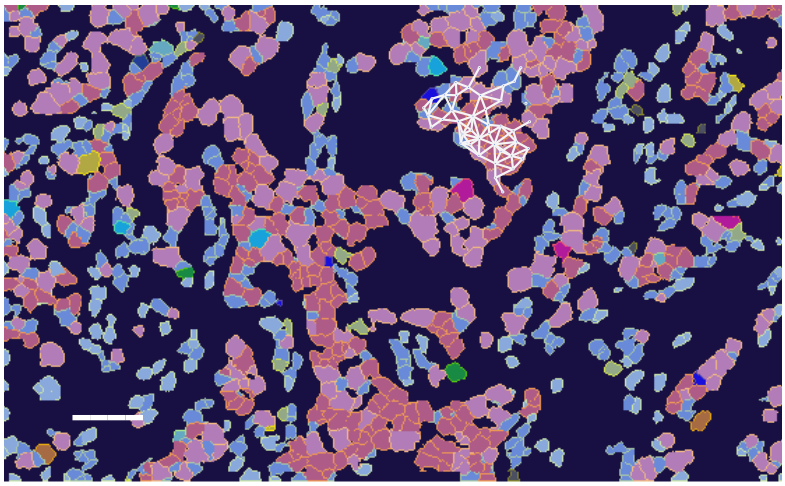
Type 26



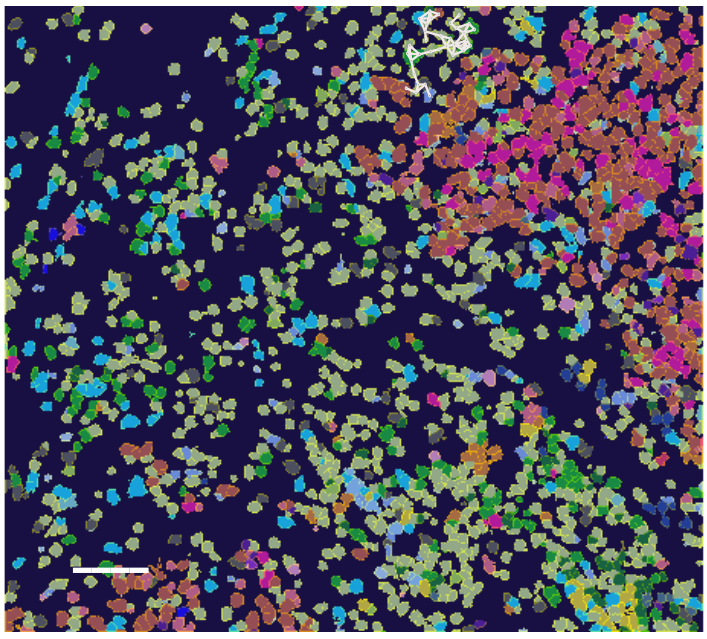
Type 27



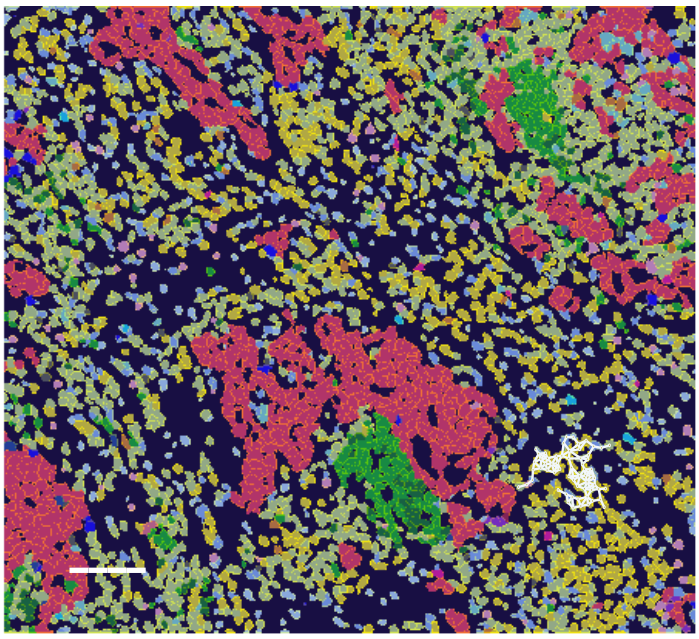
Type 28



Type 29

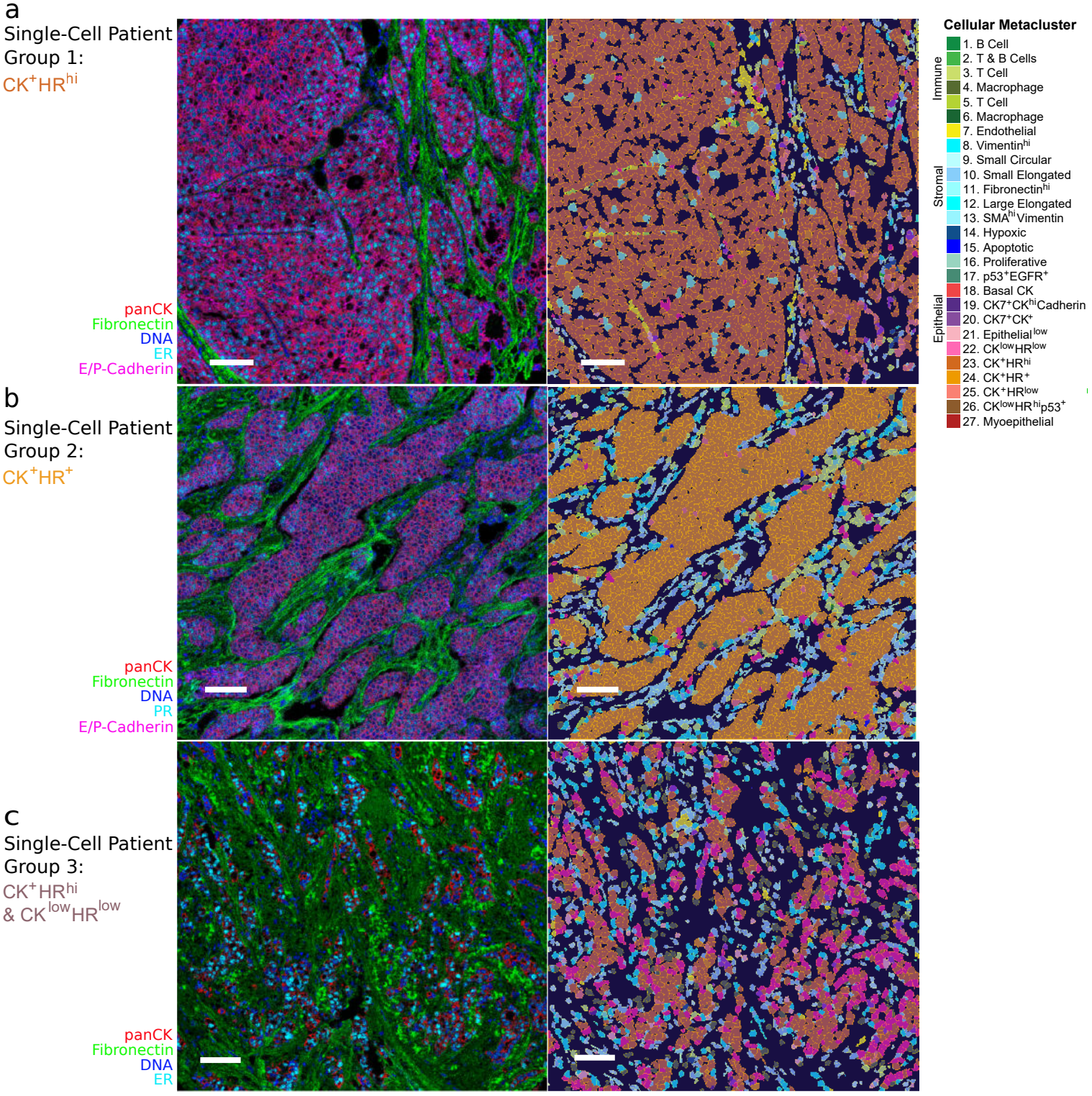


Type 30



Supplementary Images 2: Example images from different patients of the analyzed cohort, each highlighting an individual epithelial or microenvironment community type. Scale bar = 100 µm.

# Supplementary Images 3



d

Single-Cell Patient Group 4:

$CK^{+}HR^{low}$

panCK
Fibronectin
DNA
PR
E/P-Cadherin

e

Single-Cell Patient Group 5:

$CK^{+}HR^{low}$ mixed

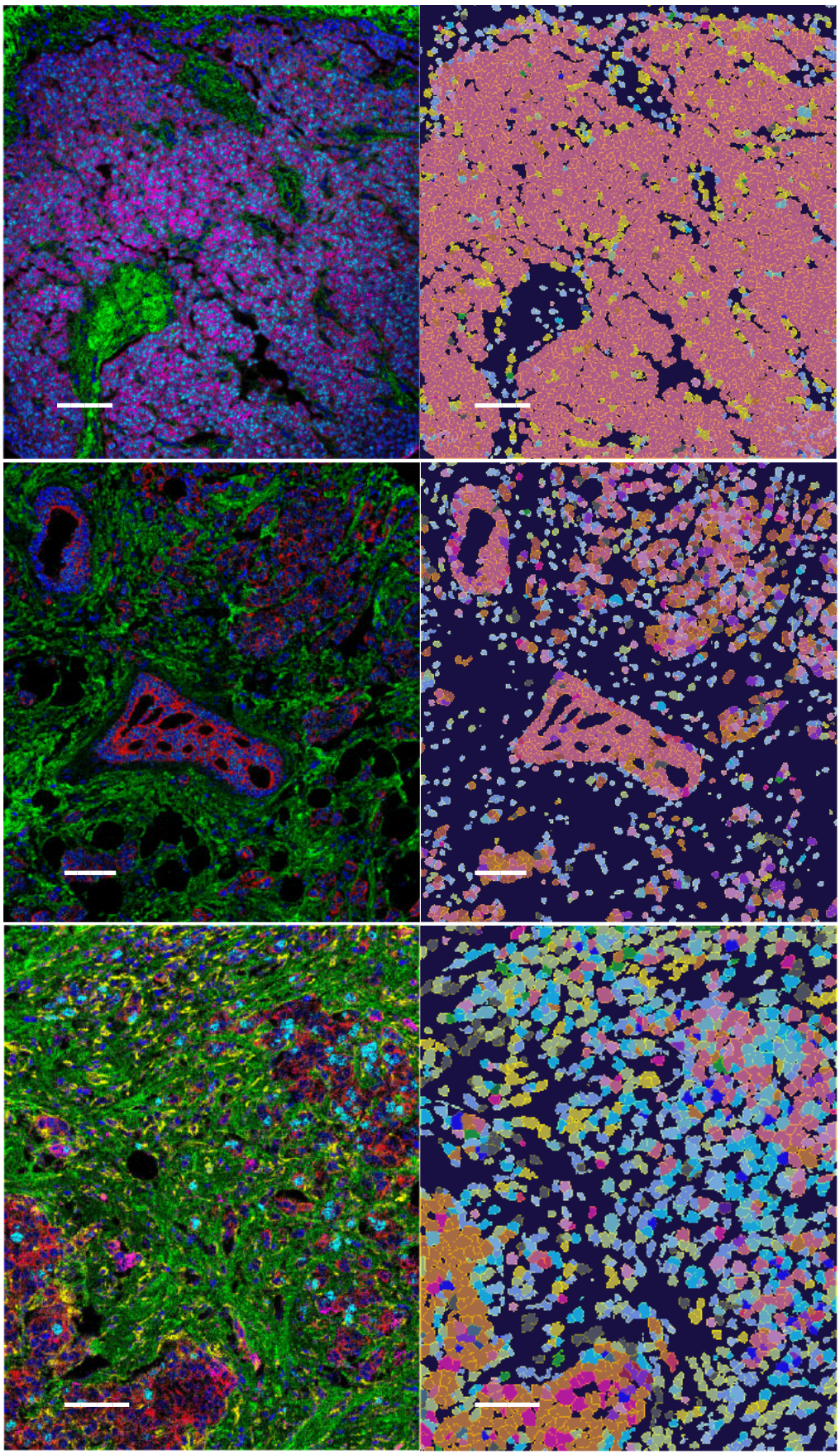
panCK
Fibronectin
DNA
ER

f

Single-Cell Patient Group 8:

Mixed

panCK
Fibronectin
DNA
Ki67
CK 14
Vimentin

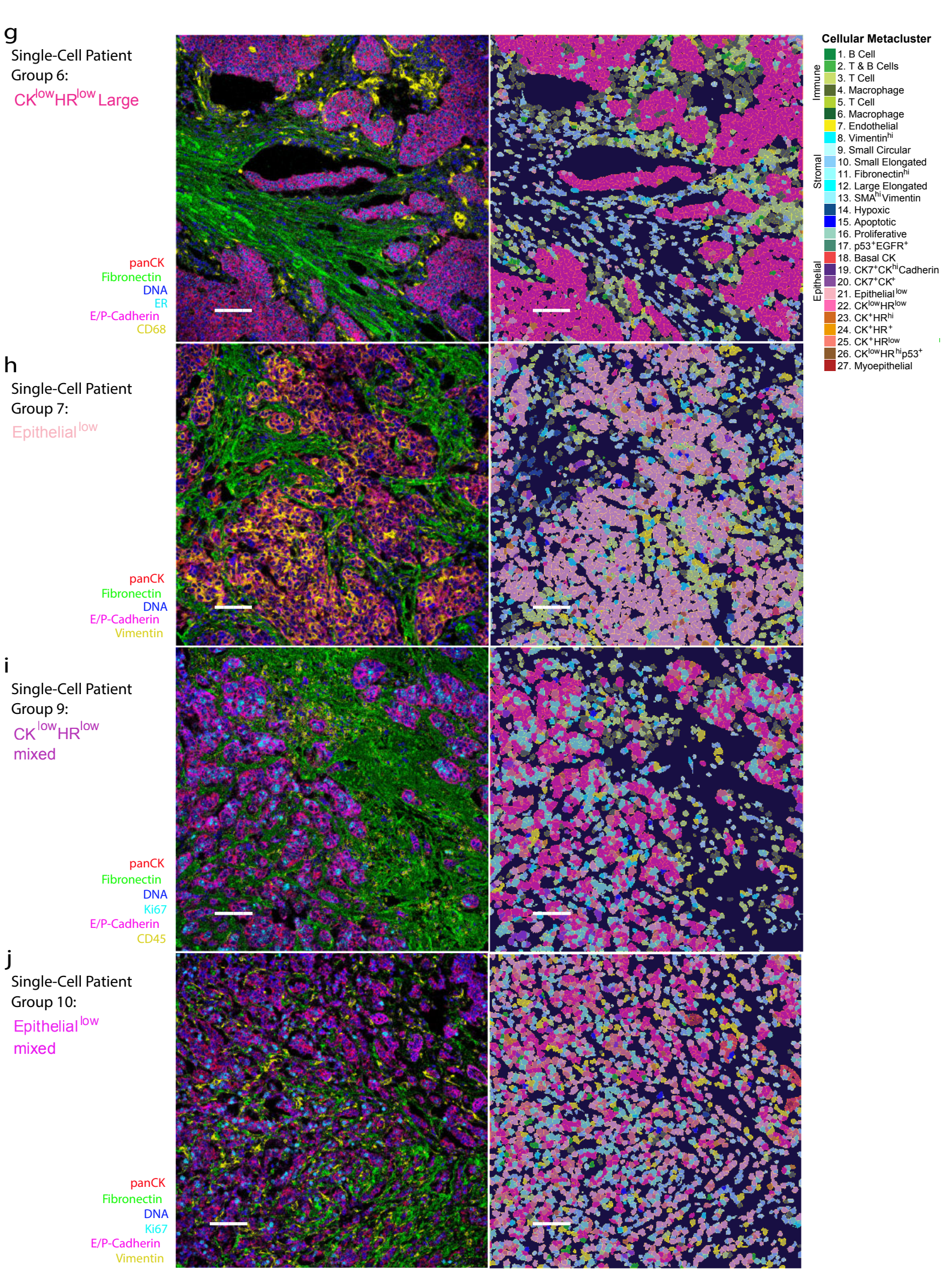


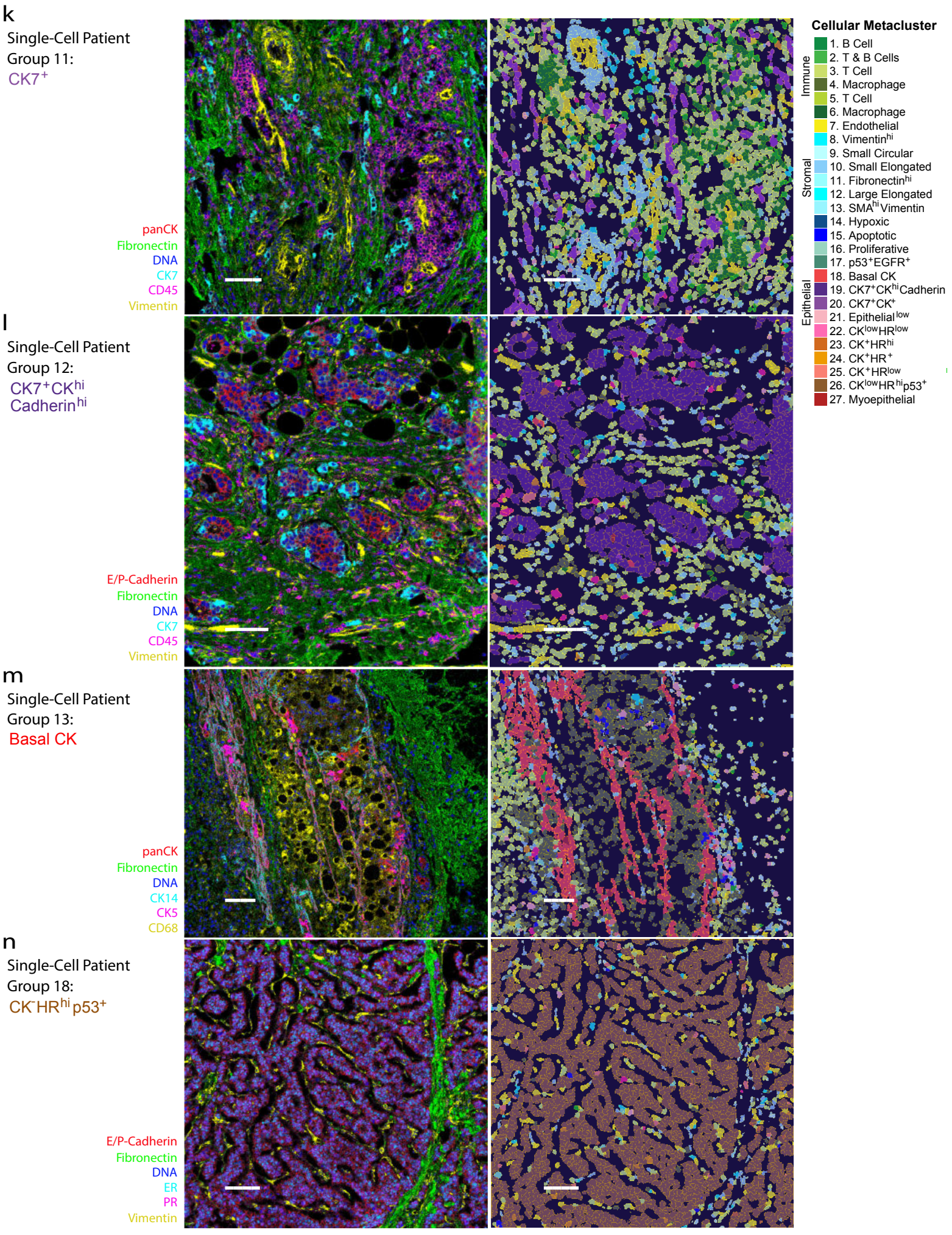
**Cellular Metacluster**

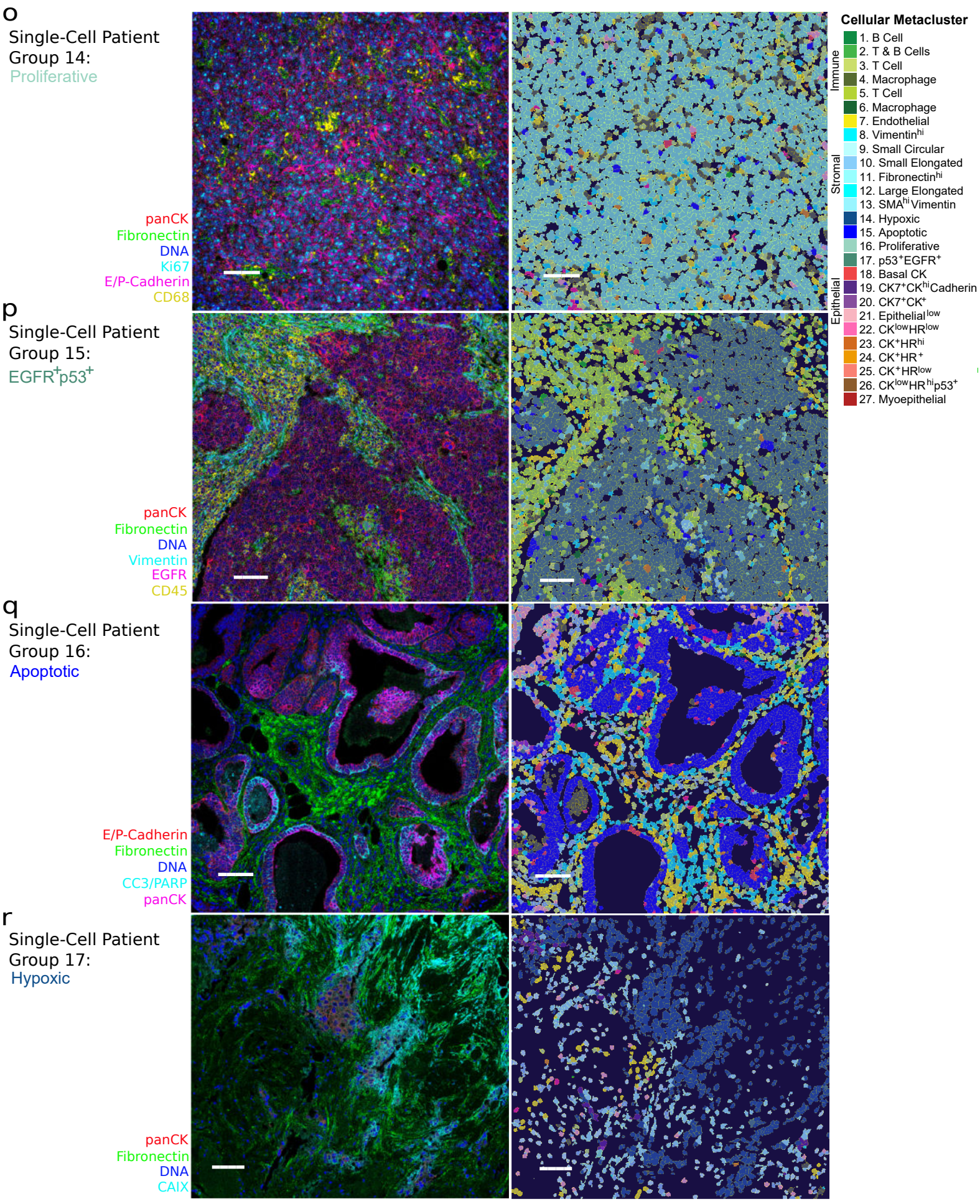
Immune
1. B Cell
2. T & B Cells
3. T Cell
4. Macrophage
5. T Cell
6. Macrophage
7. Endothelial
8. Vimentin$^{hi}$

Stromal
9. Small Circular
10. Small Elongated
11. Fibronectin$^{hi}$
12. Large Elongated
13. SMA$^{hi}$ Vimentin
14. Hypoxic
15. Apoptotic
16. Proliferative
17. p53$^{+}$EGFR$^{+}$

Epithelial
18. Basal CK
19. CK7$^{+}$CK$^{hi}$Cadherin
20. CK7$^{+}$CK$^{+}$
21. Epithelial$^{low}$
22. CK$^{low}$HR$^{low}$
23. CK$^{+}$HR$^{hi}$
24. CK$^{+}$HR$^{+}$
25. CK$^{+}$HR$^{low}$
26. CK$^{low}$HR$^{hi}$p53$^{+}$
27. Myoepithelial


g
Single-Cell Patient
Group 6:
CK^low HR^low Large
panCK
Fibronectin
DNA
ER
E/P-Cadherin
CD68
h
Single-Cell Patient
Group 7:
Epithelial^low
panCK
Fibronectin
DNA
E/P-Cadherin
Vimentin
i
Single-Cell Patient
Group 9:
CK^low HR^low
mixed
panCK
Fibronectin
DNA
Ki67
E/P-Cadherin
CD45
j
Single-Cell Patient
Group 10:
Epithelial^low
mixed
panCK
Fibronectin
DNA
Ki67
E/P-Cadherin
Vimentin
Cellular Metacluster
Immune
1. B Cell
2. T & B Cells
3. T Cell
4. Macrophage
5. T Cell
6. Macrophage
7. Endothelial
8. Vimentin^hi
Stromal
9. Small Circular
10. Small Elongated
11. Fibronectin^hi
12. Large Elongated
13. SMA^hi Vimentin
14. Hypoxic
15. Apoptotic
16. Proliferative
17. p53^+EGFR^+
Epithelial
18. Basal CK
19. CK7^+CK^hi Cadherin
20. CK7^+CK^+
21. Epithelial^low
22. CK^low HR^low
23. CK^+HR^hi
24. CK^+HR^+
25. CK^+HR^low
26. CK^low HR^hi p53^+
27. Myoepithelial


k
Single-Cell Patient
Group 11:
CK7+
panCK
Fibronectin
DNA
CK7
CD45
Vimentin
l
Single-Cell Patient
Group 12:
CK7+CKhi
Cadherinhi
E/P-Cadherin
Fibronectin
DNA
CK7
CD45
Vimentin
m
Single-Cell Patient
Group 13:
Basal CK
panCK
Fibronectin
DNA
CK14
CK5
CD68
n
Single-Cell Patient
Group 18:
CK-HRhi p53+
E/P-Cadherin
Fibronectin
DNA
ER
PR
Vimentin
Cellular Metacluster
Immune
1. B Cell
2. T & B Cells
3. T Cell
4. Macrophage
5. T Cell
6. Macrophage
7. Endothelial
8. Vimentinhi
Stromal
9. Small Circular
10. Small Elongated
11. Fibronectinhi
12. Large Elongated
13. SMAhi Vimentin
14. Hypoxic
15. Apoptotic
16. Proliferative
17. p53+EGFR+
Epithelial
18. Basal CK
19. CK7+CKhi Cadherin
20. CK7+CK+
21. Epithelialhi
22. CKlowHRlow
23. CK+HRhi
24. CK+HR+
25. CK+HRlow
26. CKlowHRhip53+
27. Myoepithelial




Supplementary Images 3: Example images representing a tumor from each SCP subgroup. (left) 6-color image of representative markers, (right) same image with single-cells colored by cell type metacluster. Scale bar = 100 μm.

**Supplementary Table 1**

| Metadata | Values | Counts/ Means |
|---|---|---|
| Grade | 1 | 38 |
| | 2 | 117 |
| | 3 | 126 |
| Tumor Size [mm] | 6 - 125 | 26.28 |
| Age [years] | 26 - 92 | 62.41 |
| Gender | Female | 281 |
| | Male | 0 |
| PTNM_M | 0 | 274 |
| | 1 | 7 |
| PTNM_T | 1 | 11 |
| | 1b | 7 |
| | 1c | 99 |
| | 2 | 132 |
| | 2a | 1 |
| | 3 | 13 |
| | 4 | 7 |
| | 4b | 11 |
| PTNM_N | 0 | 135 |
| | 0sl | 2 |
| | 0sn | 1 |
| | 1 | 32 |
| | 1mi | 9 |
| | 1a | 39 |
| | 2 | 15 |
| | 2a | 15 |
| | 3 | 7 |
| | 3a | 12 |
| | 3b | 1 |
| ER Status | Positive | 209 |
| | Negative | 72 |
| PR Status | Positive | 152 |
| | Negative | 129 |
| HER2 Status | Positive | 52 |
| | Negative | 229 |
| Pre-surgery Treatment | None | 279 |
| | Neoadjuvent Chemo | 2 |
| DFS [months] follow up | 0 - 195 | 69.85 |
| OS [months] follow up | 0 - 236 | 80.38 |
| Patient Status | Alive | 182 |
| | Alive with Metastases | 20 |
| | Death by Pimary Disease | 57 |
| | Death | 22 |
| Response to Hormone Therapy | NA | 116 |
| | Sensitive | 88 |
| | Refractory | 44 |
| | Resistant | 33 |
| Clinical Subtype | HR+HER2+ | 29 |
| | HR+HER2- | 175 |
| | HR-HER2+ | 23 |
| | TripleNeg | 48 |

**Supplementary Table 2**

| Metal Tag | Target | Antibody Clone | Company | Catalogue Number | Lot |
|---|---|---|---|---|---|
| In113 | Histone H3 | D1H2 | Cell Signaling | 4499BF | 12 |
| La139 | H3 (Lys28) trimethylate | C36B11 | Cell Signaling | 9733BF | 11 |
| Pr141 | Cytokeratin 5 | EP1601Y | Abcam | Custom | GR299320-I |
| Nd142 | Fibronectin | 10/Fibronectin | BD Biosciences | 610078 | 6251888 |
| Nd143 | Cytokeratin 19 | Troma-III | Dev Studies Hybridoma Bank | Troma -III | 2003-07-13 |
| Nd144 | Cytokeratin 8/18 | C51 | Cell Signaling | 4546BF | 2 |
| Nd145 | Twist | polyclonal_Twist1_ABD29 | Millipore | ABD29 | 2754704 |
| Nd146 | CD68 | KP1 | E-Bioscience | 14-0688-82 | E15987-105 |
| Sm147 | Keratin 14 (KRT14) | polyclonal_PA5-16722 | Thermo Fischer | PA5-16722 | SE2391461H |
| Nd148 | SMA | 1A4 | Abcam | ab7817 | 033M4768 |
| Sm149 | Vimentin | D21H3 | Cell Signaling | 5741BF | 3 |
| Nd150 | c-Myc | 90000000000 | Biolegend | 626802 | B201394 |
| Eu151 | c-erbB-2 - Her2 | 3B5 | BD Biosciences | 554299 | 6182799 |
| Sm152 | CD3 epsilon | D7A6E | Cell Signaling | 85061 | 2 |
| Eu153 | Histone H3 | HTA28 | Biolegend | 641002 | B200946 |
| Gd155 | Slug | 666633 | R&D Systems | Custom | CFZB021603A |
| Gd156 | Estrogen Receptor Alpha | EP1 | Epitomics | AC-0015EU | |
| Gd156 | Rabbit IgG (H+L) | polyclonal_AI-1000 | Vector Labs | AI-1000 | ZA0911 |
| Gd158 | Progesterone Receptor A/B | SP2 | Spring Bioscience | M3024 C | 131017 |
| Gd158 | Progesterone Receptor A/B | EP2 | Epitomics | AC-0028EU | |
| Tb159 | p53 | 7F5 | Cell Signaling | 2527BF | 5 |
| Gd160 | CD44 | polyclonal_CD44 | R&D Systems | AF3660 | CFOE0216011 |
| Dy162 | CD45 | 2B11 | E-Bioscience | 14-9457-82 | 4298126 |
| Dy163 | GATA3 | L50-823 | BD Biosceinces | 558686 | 6132744 |
| Dy164 | CD20 | L26 | E-Bioscience | 14-0202-82 | 4285442 |
| Er166 | Carbonic Anhydrase IX | polyclonal_CAIX | R&D Systems | AF2188 | VNQ0215032 |
| Er167 | E-Cadherin / P-Cadherin | 36/E-Cadherin | BD Biosciences | 610182 | 6251878 |
| Er168 | Ki-67 | 8D5 | Cell Signaling | 9449BF | 2 |
| Tm169 | EGFR | D38B1 | Cell Signaling | 4267BF | 13 |
| Yb170 | p-S6 | D57.2.2E | Cell Signaling | 4858BF | 15 |

| | | | | | |
|---|---|---|---|---|---|
| Yb172 | vWF | poly vwf | Millipore | AB7356 | 2700933 |
| Yb172 | CD31 | JC70A | Novus Biologicals | NB600-562 | B-1 |
| Yb173 | p-mTOR | 49F9 | Cell Signaling | 2976 | 11 |
| Yb174 | Cytokeratin 7 | RCK105 | BD Biosciences | 550507 | 6083676 |
| Lu175 | pan Cytokeratin | AE1 | Millipore | MAB1612 | 2341224 |
| Lu175 | pan Cytokeratin | AE3 | Millipore | MAB1611 | 2607604 |
| Yb176 | cleaved PARP | F21-852 | BD Biosciences | 552596 | 2150663 |
| Yb176 | Cleaved Caspase3 | C92-605 | BD Biosciences | 559565 | 6074683 |

**Supplementary Table 3**

| Single-Cell Pathology Patient Group | Nr. Patients | Tumor Size [mm] Mean | Tumor Size [mm] STD | Age [y] Mean | Grade 1 | Grade 2 | Grade 3 | PTNM_M 0 | PTNM_M 1 |
|---|---|---|---|---|---|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | 17 | 23.0 | 11.4 | 67.5 | 5 | 9 | 3 | 16 | 1 |
| **2** $CK^{+}$ $HR^{+}$ | 21 | 22.3 | 10.3 | 60.4 | 4 | 13 | 4 | 21 | |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 20 | 21.4 | 7.3 | 64.4 | 4 | 9 | 7 | 19 | 1 |
| 4 $CK^{+}$ $HR^{low}$ | 12 | 26.5 | 20.0 | 66.8 | | 9 | 3 | 11 | 1 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 32 | 23.8 | 11.6 | 60.7 | 10 | 13 | 9 | 32 | |
| **6** $CK^{low}$ $HR^{low}$ Large | 10 | 27.7 | 8.4 | 65.3 | | 4 | 6 | 10 | |
| **7** $Epithelial^{low}$ | 13 | 25.0 | 9.9 | 63.8 | 1 | 6 | 6 | 13 | |
| **8** Mixed | 11 | 21.0 | 11.0 | 60.8 | | 5 | 6 | 11 | |
| **9** $CK^{low}$ $HR^{low}$ mixed | 20 | 30.0 | 20.4 | 62.0 | 1 | 8 | 11 | 19 | 1 |
| **10** $Epithelial^{low}$ mixed | 24 | 26.6 | 12.2 | 60.2 | 3 | 12 | 9 | 22 | 2 |
| **11** $CK7^{+}$ | 31 | 29.4 | 16.5 | 63.9 | 6 | 15 | 10 | 31 | |
| **12** $CK7^{+}$ $CK^{hi}$ $E/P\text{-}Cadherin^{hi}$ | 14 | 26.5 | 21.2 | 60.4 | 3 | 6 | 5 | 13 | 1 |
| **13** Basal CK | 15 | 32.2 | 25.9 | 60.7 | | 4 | 11 | 15 | |
| **14** Proliferative | 11 | 35.2 | 30.9 | 59.3 | | 1 | 10 | 11 | |
| **15** $EGFR^{+}$ $p53^{+}$ | 8 | 22.6 | 6.6 | 64.0 | | | 8 | 8 | |
| **16** Apoptotic | 10 | 28.2 | 10.6 | 58.9 | 1 | 2 | 7 | 10 | |
| **17** Hypoxic | 9 | 26.6 | 12.1 | 61.2 | | | 9 | 9 | |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | 3 | 40.3 | 18.5 | 71.3 | | 1 | 2 | 3 | |

| **Single-Cell Pathology** | PTNM_N | PTNM_N | PTNM_N | PTNM_N | PTNM_N | PTNM_N | PTNM_N | PTNM_N | PTNM_N | PTNM_N |
|---|---|---|---|---|---|---|---|---|---|---|
| **Patient Group** | 0 | 0sl | 0sn | 1 | 1a | 1mi | 2 | 2a | 3 | 3a |
| **1** $CK^{+}$ $Hr^{hi}$ | 7 | | | 4 | 3 | | | | 1 | |
| **2** $CK^{+}$ $HR^{+}$ | 12 | | | 3 | | 1 | 1 | 2 | | |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 7 | | | 3 | 5 | | 1 | 1 | 2 | 1 |
| 4 $CK^{+}$ $HR^{low}$ | 6 | | | 3 | 2 | | | | | |
| **5** $CK^{+}$ $HR^{low}$ mixed | 17 | 1 | | 2 | 4 | 1 | 2 | 2 | | 1 |
| **6** $CK^{low}$ $HR^{low}$ Large | 2 | | | 1 | 1 | 1 | 2 | | 1 | 1 |
| **7** $Epithelial^{low}$ | 7 | | 1 | 1 | | 2 | 1 | | | |
| **8** Mixed | 4 | | | 1 | 1 | 1 | 1 | | | 3 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 7 | | | 3 | 3 | | 2 | 2 | | 1 |
| **10** $Epithelial^{low}$ mixed | 11 | 1 | | 3 | 4 | 1 | | 4 | | |
| **11** $CK7^{+}$ | 16 | | | 3 | 4 | | 1 | 3 | 1 | 3 |
| **12** $CK7^{+}$ $CK^{hi}$ $E/P\text{-}Cadherin^{hi}$ | 11 | | | 2 | | | | | 1 | |
| **13** Basal CK | 7 | | | | 2 | 1 | | | | 2 |
| **14** Proliferative | 5 | | | | 3 | 1 | 1 | | 1 | |
| **15** $EGFR^{+}$ $p53^{+}$ | 5 | | | 1 | | | 2 | | | |
| **16** Apoptotic | 6 | | | | 4 | | | | | |
| **17** Hypoxic | 4 | | | 2 | 3 | | | | | |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | 1 | | | | | | 1 | 1 | | |

| **Single-Cell Pathology Patient Group** | PTNM_N 3b | Clinical Type HR+HER2+ | Clinical Type HR+HER2- | Clinical Type HR-HER2+ | Clinical Type Triple Negative | Clinical Type NA | Patient Status Alive |
|---|---|---|---|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | | 2 | 15 | | | | 10 |
| **2** $CK^{+}$ $HR^{+}$ | | 7 | 10 | 1 | 2 | 1 | 13 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | | 1 | 18 | | | 1 | 10 |
| 4 $CK^{+}$ $HR^{low}$ | | 1 | 10 | | 1 | | 7 |
| **5** $CK^{+}$ $HR^{low}$ mixed | | 1 | 30 | | | 1 | 23 |
| **6** $CK^{low}$ $HR^{low}$ Large | | 2 | 8 | | | | 5 |
| **7** $Epithelial^{low}$ | | | 8 | 2 | 2 | 1 | 6 |
| **8** Mixed | | 1 | 4 | | 6 | | 5 |
| **9** $CK^{low}$ $HR^{low}$ mixed | | 5 | 11 | 2 | 2 | | 12 |
| **10** $Epithelial^{low}$ mixed | | 6 | 16 | 1 | 1 | | 16 |
| **11** $CK7^{+}$ | | | 19 | 10 | 2 | | 28 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | | 1 | 11 | | 2 | | 8 |
| **13** Basal CK | 1 | | 5 | 4 | 6 | | 10 |
| **14** Proliferative | | | 3 | | 7 | 1 | 6 |
| **15** $EGFR^{+}$ $p53^{+}$ | | | | | 8 | | 7 |
| **16** Apoptotic | | 1 | 2 | 1 | 6 | | 10 |
| **17** Hypoxic | | 1 | 3 | 2 | 3 | | 5 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | | 2 | | | 1 | 1 |

| **Single-Cell Pathology Patient Group** | Patient Status Alive w Metastases | Patient Status Death | Patient Status Death by Primary Disease | Response NA | Response Refractory | Response Resistant |
|---|---|---|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | 3 | 4 | | 5 | 2 | 3 |
| **2** $CK^{+}$ $HR^{+}$ | 4 | | 4 | 7 | 4 | 4 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 2 | 1 | 7 | 3 | 5 | 5 |
| 4 $CK^{+}$ $HR^{low}$ | 1 | 1 | 3 | 2 | 2 | 3 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 1 | 3 | 5 | 6 | 5 | 2 |
| **6** $CK^{low}$ $HR^{low}$ Large | 1 | | 4 | 3 | 3 | 2 |
| **7** $Epithelial^{low}$ | 2 | 1 | 4 | 4 | 1 | 4 |
| **8** Mixed | | | 6 | 6 | 3 | 1 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 2 | 3 | 3 | 8 | 2 | 3 |
| **10** $Epithelial^{low}$ mixed | 2 | 2 | 4 | 10 | 7 | 1 |
| **11** $CK7^{+}$ | | 2 | 1 | 16 | | 2 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 1 | 1 | 4 | 5 | 3 | 2 |
| **13** Basal CK | 1 | 1 | 3 | 12 | 1 | |
| **14** Proliferative | | 1 | 4 | 7 | 2 | |
| **15** $EGFR^{+}$ $p53^{+}$ | | | 1 | 8 | | |
| **16** Apoptotic | | | | 7 | | |
| **17** Hypoxic | | 1 | 3 | 6 | 2 | 1 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | 1 | 1 | 1 | 2 | |

| **Single-Cell Pathology Patient Group** | Response Sensitive | Post-surgery Treatment Anastrazol | Post-surgery Treatment Chemo | Post-surgery Treatment Chemo - Anastrazol |
|---|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | 7 | 1 | | |
| **2** $CK^{+}$ $HR^{+}$ | 6 | 2 | 1 | |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 7 | 2 | | |
| 4 $CK^{+}$ $HR^{low}$ | 5 | 3 | | |
| **5** $CK^{+}$ $HR^{low}$ mixed | 19 | 2 | | |
| **6** $CK^{low}$ $HR^{low}$ Large | 2 | 1 | 1 | 1 |
| **7** $Epithelial^{low}$ | 4 | 1 | | |
| **8** Mixed | 1 | 1 | 1 | 1 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 7 | 1 | 3 | 1 |
| **10** $Epithelial^{low}$ mixed | 6 | 1 | 1 | 1 |
| **11** $CK7^{+}$ | 13 | 4 | 6 | 1 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 4 | 1 | 1 | 1 |
| **13** Basal CK | 2 | | 5 | |
| **14** Proliferative | 2 | | 4 | |
| **15** $EGFR^{+}$ $p53^{+}$ | | | 5 | |
| **16** Apoptotic | 3 | | 4 | |
| **17** Hypoxic | | | 3 | |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | | | |

| **Single-Cell Pathology Patient Group** | Post-surgery Treatment Chemo - Hormone Therapy | Post-surgery Treatment Chemo - Immune Therapy | Post-surgery Treatment Chemo - Immune Therapy - Anastrozol |
|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | 1 | | 1 |
| **2** $CK^{+}$ $HR^{+}$ | 1 | | |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | | | |
| 4 $CK^{+}$ $HR^{low}$ | 1 | | |
| **5** $CK^{+}$ $HR^{low}$ mixed | 1 | | |
| **6** $CK^{low}$ $HR^{low}$ Large | | | |
| **7** $Epithelial^{low}$ | 1 | 1 | |
| **8** Mixed | | | |
| **9** $CK^{low}$ $HR^{low}$ mixed | 1 | | |
| **10** $Epithelial^{low}$ mixed | | | 1 |
| **11** $CK7^{+}$ | | 2 | |
| **12** $CK7^{+}$ $CK^{hi}$ $E/P\text{-}Cadherin^{hi}$ | 1 | | |
| **13** Basal CK | | 2 | |
| **14** Proliferative | | | |
| **15** $EGFR^{+}$ $p53^{+}$ | | | |
| **16** Apoptotic | | 1 | |
| **17** Hypoxic | | 1 | |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | | |

| **Single-Cell Pathology Patient Group** | Post-surgery Treatment Chemo - Immune Therapy - Tamoxifen | Post-surgery Treatment Chemo - Letrozol | Post-surgery Treatment Chemo - Tamoxifen |
|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | | 2 | |
| **2** $CK^{+}$ $HR^{+}$ | | | 3 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | | | 4 |
| 4 $CK^{+}$ $HR^{low}$ | | | 1 |
| **5** $CK^{+}$ $HR^{low}$ mixed | | | 5 |
| **6** $CK^{low}$ $HR^{low}$ Large | | | 1 |
| **7** $Epithelial^{low}$ | | 1 | 2 |
| **8** Mixed | | | 2 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 1 | 1 | 1 |
| **10** $Epithelial^{low}$ mixed | | 2 | 3 |
| **11** $CK7^{+}$ | | 1 | 1 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | | | 1 |
| **13** Basal CK | | | |
| **14** Proliferative | | | |
| **15** $EGFR^{+}$ $p53^{+}$ | | | |
| **16** Apoptotic | | | |
| **17** Hypoxic | | | 2 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | | |

| **Single-Cell Pathology Patient Group** | Post-surgery Treatment Exemestan | Post-surgery Treatment Hormone Therapy | Post-surgery Treatment Immune Therapy | Post-surgery Treatment Immune Therapy - Anastrozol |
|---|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | | 1 | | |
| **2** $CK^{+}$ $HR^{+}$ | | 7 | | |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | | 6 | | |
| 4 $CK^{+}$ $HR^{low}$ | | 1 | | |
| **5** $CK^{+}$ $HR^{low}$ mixed | 1 | 1 | | |
| **6** $CK^{low}$ $HR^{low}$ Large | | | | |
| **7** $Epithelial^{low}$ | | 1 | 1 | |
| **8** Mixed | | | | |
| **9** $CK^{low}$ $HR^{low}$ mixed | | | | |
| **10** $Epithelial^{low}$ mixed | | | 1 | 1 |
| **11** $CK7^{+}$ | | | 3 | |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | | 1 | | |
| **13** Basal CK | | | 1 | |
| **14** Proliferative | | 1 | | |
| **15** $EGFR^{+}$ $p53^{+}$ | | | | |
| **16** Apoptotic | | 2 | | |
| **17** Hypoxic | | | | |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | 1 | | |

| **Single-Cell Pathology Patient Group** | Post-surgery Treatment Letrozol | Post-surgery Treatment Tamoxifen | Post-surgery Treatment Tamoxifen - Femara | Post-surgery Treatment None |
|---|---|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | 1 | 9 | | 1 |
| **2** $CK^{+}$ $HR^{+}$ | 1 | 2 | | 3 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | | 8 | | |
| 4 $CK^{+}$ $HR^{low}$ | 1 | 4 | | 1 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 1 | 20 | | 1 |
| **6** $CK^{low}$ $HR^{low}$ Large | | 6 | | |
| **7** $Epithelial^{low}$ | 1 | 2 | | 1 |
| **8** Mixed | | 2 | | 2 |
| **9** $CK^{low}$ $HR^{low}$ mixed | | 8 | | 1 |
| **10** $Epithelial^{low}$ mixed | | 11 | 1 | 1 |
| **11** $CK7^{+}$ | 1 | 9 | | 2 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | | 7 | | |
| **13** Basal CK | 1 | 2 | | 3 |
| **14** Proliferative | | 3 | | 2 |
| **15** $EGFR^{+}$ $p53^{+}$ | | | | |
| **16** Apoptotic | | 2 | | 1 |
| **17** Hypoxic | 1 | | | 1 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | | 1 | | |

| **Single-Cell Pathology Patient Group** | Pre-surgery Treatment Neoadjuvant Chemo | Pre-surgery Treatment None |
|---|---|---|
| **1** $CK^{+}$ $Hr^{hi}$ | | 17 |
| **2** $CK^{+}$ $HR^{+}$ | | 21 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | | 20 |
| 4 $CK^{+}$ $HR^{low}$ | | 12 |
| **5** $CK^{+}$ $HR^{low}$ mixed | | 32 |
| **6** $CK^{low}$ $HR^{low}$ Large | | 10 |
| **7** $Epithelial^{low}$ | | 13 |
| **8** Mixed | 1 | 10 |
| **9** $CK^{low}$ $HR^{low}$ mixed | | 20 |
| **10** $Epithelial^{low}$ mixed | | 24 |
| **11** $CK7^{+}$ | | 31 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | | 14 |
| **13** Basal CK | | 15 |
| **14** Proliferative | | 11 |
| **15** $EGFR^{+}$ $p53^{+}$ | | 8 |
| **16** Apoptotic | | 10 |
| **17** Hypoxic | | 9 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ | 1 | 2 |

**Supplementary Table 4**

**a)**

| **Single-Cell Pathology** | Coxph **Group vs All Others**, n = 278, number of events = 56 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | Nr. Patients | coef | exp(coef) | se(coef) | lower .95 | upper .95 | z | Pr(>\|z\|) |
| **1** $CK^{+}$ $HR^{hi}$ | 17 | -18.14 | 0.00 | 4029.00 | 0.00 | Inf | -0.01 | NA |
| **2** $CK^{+}$ $HR^{+}$ | 21 | -0.19 | 0.82 | 0.52 | 0.30 | 2.28 | -0.37 | 0.7090 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 20 | 0.41 | 1.51 | 0.41 | 0.68 | 3.35 | 1.02 | 0.3080 |
| 4 $CK^{+}$ $HR^{low}$ | 12 | 0.36 | 1.43 | 0.60 | 0.45 | 4.62 | 0.61 | 0.5450 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 32 | -0.64 | 0.53 | 0.47 | 0.21 | 1.33 | -1.36 | 0.1750 |
| **6** $CK^{low}$ $HR^{low}$ | 10 | 0.86 | 2.37 | 0.52 | 0.86 | 6.57 | 1.66 | 0.0962 |
| **7** $Epithelial^{low}$ | 13 | 0.44 | 1.56 | 0.52 | 0.56 | 4.31 | 0.85 | 0.3940 |
| **8** Mixed | 11 | 1.46 | 4.30 | 0.43 | 1.84 | 10.06 | 3.37 | 0.0008 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 20 | -0.21 | 0.81 | 0.59 | 0.25 | 2.59 | -0.36 | 0.7180 |
| **10** $Epithelial^{low}$ mixed | 24 | -0.32 | 0.73 | 0.52 | 0.26 | 2.01 | -0.61 | 0.5390 |
| **11** $CK7^{+}$ | 31 | -1.98 | 0.14 | 1.01 | 0.02 | 1.00 | -1.97 | 0.0495 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 14 | 0.81 | 2.26 | 0.53 | 0.81 | 6.32 | 1.55 | 0.1210 |
| **13** Basal CK | 15 | 0.07 | 1.07 | 0.59 | 0.33 | 3.44 | 0.12 | 0.9040 |
| **14** Proliferative | 11 | 1.05 | 2.85 | 0.52 | 1.03 | 7.91 | 2.02 | 0.0439 |
| **15** $EGFR^{+}$ $p53^{+}$ | 8 | 0.50 | 1.65 | 1.01 | 0.23 | 11.98 | 0.49 | 0.6220 |
| **16** Apoptotic | 10 | -17.06 | 0.00 | 3663.00 | 0.00 | Inf | -0.01 | NA |
| **17** Hypoxic | 9 | 0.94 | 2.57 | 0.60 | 0.80 | 8.27 | 1.58 | 0.1140 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ *excluded* | *3* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |

**b)**

| **Single-Cell Pathology** | Coxph **Group vs Similar Groups** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient Groups** | Nr. Patients | Nr. Events | coef | exp(coef) | se(coef) | lower .95 | upper .95 | z | Pr(>\|z\|) |
| **1 vs 2,3** | 58 | 11 | -19.57 | 0.00 | 8303.00 | 0.00 | Inf | 0.00 | NA |
| **3 vs 1,2** | 58 | 11 | 1.17 | 3.23 | 0.63 | 0.94 | 11.02 | 1.87 | 0.0618 |
| **16 vs 13,14,15,17** | 53 | 11 | -19.44 | 0.00 | 9088.00 | 0.00 | Inf | 0.00 | NA |
| **11 vs 12** | 45 | 5 | -2.62 | 0.07 | 1.14 | 0.01 | 0.68 | -2.30 | 0.0200 |

**c)**

| **Single-Cell Pathology** | Coxph **within HR+HER2-**, Group vs All Others, n = 173, number of events = 29 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | Nr. Patients | coef | exp(coef) | se(coef) | lower .95 | upper .95 | z | Pr(>\|z\|) |
| **1** $CK^{+}$ $HR^{hi}$ | 15 | -18.17 | 0.00 | 5085.00 | 0.00 | Inf | 0.00 | NA |
| **2** $CK^{+}$ $HR^{+}$ | 10 | -17.11 | 0.00 | 3736.00 | 0.00 | Inf | -0.01 | NA |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 18 | 0.52 | 1.69 | 0.49 | 0.64 | 4.44 | 1.06 | 0.2880 |
| 4 $CK^{+}$ $HR^{low}$ | 10 | 0.36 | 1.43 | 0.74 | 0.34 | 6.09 | 0.49 | 0.6270 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 30 | -0.49 | 0.61 | 0.54 | 0.21 | 1.77 | -0.90 | 0.3660 |
| **6** $CK^{low}$ $HR^{low}$ | 8 | 1.04 | 2.83 | 0.61 | 0.85 | 9.37 | 1.70 | 0.0893 |
| **7** $Epithelial^{low}$ | 8 | 0.41 | 1.51 | 0.73 | 0.36 | 6.37 | 0.56 | 0.5750 |
| **8** mixed | 4 | 1.14 | 3.12 | 0.73 | 0.74 | 13.17 | 1.55 | 0.1210 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 11 | -0.42 | 0.66 | 1.02 | 0.09 | 4.85 | -0.41 | 0.6820 |
| **10** $Epithelial^{low}$ mixed | 16 | -0.32 | 0.73 | 0.73 | 0.17 | 3.08 | -0.43 | 0.6670 |
| **11** $CK7^{+}$ | 19 | -18.21 | 0.00 | 4516.00 | 0.00 | Inf | 0.00 | NA |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 11 | 1.03 | 2.79 | 0.62 | 0.82 | 9.48 | 1.65 | 0.0996 |
| **13** Basal CK | 5 | 0.02 | 1.02 | 1.02 | 0.14 | 7.53 | 0.02 | 0.9840 |
| **14** Proliferative | 3 | 2.30 | 10.00 | 0.75 | 2.30 | 43.54 | 3.07 | 0.0022 |
| **15** $EGFR^{+}$ $p53^{+}$ | 0 | NA | NA | NA | NA | NA | NA | NA |
| **16** Apoptotic | 2 | -16.02 | 0.00 | 4880.00 | 0.00 | Inf | 0.00 | NA |
| **17** Hypoxic | 3 | 1.90 | 6.68 | 0.74 | 1.57 | 28.40 | 2.57 | 0.0101 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ *excluded* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |

**d)**

| **Single-Cell Pathology** | Logrank **Group vs All Others** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V | Chisq | DF | P |
| **1** $CK^+$ $HR^{hi}$ | 17 | 0 | 4.25 | 4.25 | 4.25 | | | |
| | 261 | 56 | 51.75 | 0.35 | 0.35 | 4.60 | 1 | 0.0300 |
| **2** $CK^+$ $HR^+$ | 21 | 4 | 4.78 | 0.13 | 0.14 | | | |
| | 257 | 52 | 51.22 | 0.01 | 0.14 | 0.10 | 1 | 0.7000 |
| **3** $CK^+$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 20 | 7 | 4.84 | 0.97 | 1.07 | | | |
| | 258 | 49 | 51.16 | 0.09 | 1.07 | 1.10 | 1 | 0.3000 |
| 4 $CK^+$ $HR^{low}$ | 12 | 3 | 2.14 | 0.35 | 0.36 | | | |
| | 266 | 53 | 53.86 | 0.01 | 0.36 | 0.40 | 1 | 0.5000 |
| **5** $CK^+$ $HR^{low}$ mixed | 32 | 5 | 8.70 | 1.57 | 1.90 | | | |
| | 246 | 51 | 47.30 | 0.29 | 1.90 | 1.90 | 1 | 0.2000 |
| **6** $CK^{low}$ $HR^{low}$ | 10 | 4 | 1.76 | 2.86 | 2.97 | | | |
| | 268 | 52 | 54.24 | 0.09 | 2.97 | 3.00 | 1 | 0.0800 |
| **7** $Epithelial^{low}$ | 13 | 4 | 2.65 | 0.69 | 0.73 | | | |
| | 265 | 52 | 53.35 | 0.03 | 0.73 | 0.70 | 1 | 0.4000 |
| **8** mixed | 11 | 6 | 1.55 | 12.74 | 13.20 | | | |
| | 267 | 50 | 54.45 | 0.36 | 13.20 | 13.20 | 1 | 0.0003 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 20 | 3 | 3.66 | 0.12 | 0.13 | | | |
| | 258 | 53 | 52.34 | 0.01 | 0.13 | 0.10 | 1 | 0.7000 |
| **10** $Epithelial^{low}$ mixed | 24 | 4 | 5.36 | 0.34 | 0.38 | | | |
| | 254 | 52 | 50.64 | 0.03 | 0.38 | 0.40 | 1 | 0.5000 |
| **11** $CK7^+$ | 31 | 1 | 6.51 | 4.67 | 5.31 | | | |
| | 247 | 55 | 49.49 | 0.61 | 5.31 | 5.30 | 1 | 0.0200 |
| **12** $CK7^+$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 14 | 4 | 1.87 | 2.42 | 2.54 | | | |
| | 264 | 52 | 54.13 | 0.08 | 2.54 | 2.50 | 1 | 0.1000 |
| **13** Basal CK | 15 | 3 | 2.80 | 0.01 | 0.02 | | | |
| | 263 | 53 | 53.20 | 0.00 | 0.02 | 0.00 | 1 | 0.9000 |
| **14** Proliferative | 11 | 4 | 1.47 | 4.34 | 4.49 | | | |
| | 267 | 52 | 54.53 | 0.12 | 4.49 | 4.50 | 1 | 0.0300 |
| **15** $EGFR^+$ $p53^+$ | 8 | 1 | 0.61 | 0.25 | 0.25 | | | |
| | 270 | 55 | 55.39 | 0.00 | 0.25 | 0.30 | 1 | 0.6000 |
| **16** Apoptotic | 10 | 0 | 1.83 | 1.83 | 1.91 | | | |
| | 268 | 56 | 54.17 | 0.06 | 1.91 | 1.90 | 1 | 0.2000 |
| **17** Hypoxic | 9 | 3 | 1.22 | 2.61 | 2.70 | | | |
| | 269 | 53 | 54.78 | 0.06 | 2.70 | 2.70 | 1 | 0.1000 |
| **18** $CK^-$ $HR^{hi}$ $p53^+$ *excluded* | *NA* | *NA* | *NA* | *NA* | *NA* | | | |
| | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |

**e)**

| **Single-Cell Pathology** | Logrank **Group vs Similar Groups** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Groups** | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V | Chisq | DF | P |
| **1 vs** | 17 | 0 | 3.23 | 3.23 | 4.58 | | | |
| **2,3** | 41 | 11 | 7.77 | 1.34 | 4.58 | 4.60 | 1 | 0.0300 |
| **3 vs** | 20 | 7 | 3.87 | 2.52 | 3.91 | | | |
| **1,2** | 38 | 4 | 7.13 | 1.37 | 3.91 | 3.90 | 1 | 0.0500 |
| **16 vs** | 10 | 0 | 2.56 | 2.56 | 3.36 | | | |
| **13,14,15,17** | 43 | 11 | 8.44 | 0.78 | 3.36 | 3.40 | 1 | 0.0700 |
| **11 vs** | 31 | 1 | 3.79 | 2.05 | 8.67 | | | |
| **12** | 14 | 4 | 1.21 | 6.43 | 8.67 | 8.70 | 1 | 0.0030 |

**f)**

| **Single-Cell Pathology** | Logrank **within HR+HER2-,** Group vs All Others | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V | Chisq | DF | P |
| **1** $CK^+$ $HR^{hi}$ | 15 | 0 | 2.69 | 2.69 | 3.00 | | | |
| | 158 | 29 | 26.31 | 0.28 | 3.00 | 3.00 | 1 | 0.0800 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **2** $CK^{+}$ $HR^{+}$ | 10 | 0 | 1.80 | 1.80 | 1.93 | | | |
| | 163 | 29 | 27.20 | 0.12 | 1.93 | 1.90 | 1 | 0.2000 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 18 | 5 | 3.19 | 1.03 | 1.17 | | | |
| | 155 | 24 | 25.81 | 0.13 | 1.17 | 1.20 | 1 | 0.3000 |
| 4 $CK^{+}$ $HR^{low}$ | 10 | 2 | 1.44 | 0.22 | 0.23 | | | |
| | 163 | 27 | 27.56 | 0.01 | 0.23 | 0.20 | 1 | 0.6000 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 30 | 4 | 5.97 | 0.65 | 0.84 | | | |
| | 143 | 25 | 23.03 | 0.17 | 0.84 | 0.80 | 1 | 0.4000 |
| **6** $CK^{low}$ $HR^{low}$ | 8 | 3 | 1.14 | 3.04 | 3.19 | | | |
| | 165 | 26 | 27.86 | 0.12 | 3.19 | 3.20 | 1 | 0.0700 |
| **7** $Epithelial^{low}$ | 8 | 2 | 1.73 | 0.29 | 0.31 | | | |
| | 165 | 27 | 27.63 | 0.01 | 0.31 | 0.30 | 1 | 0.6000 |
| **8** Mixed | 4 | 2 | 0.69 | 2.52 | 2.60 | | | |
| | 169 | 27 | 28.31 | 0.06 | 2.60 | 2.60 | 1 | 0.1000 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 11 | 1 | 1.49 | 0.16 | 0.17 | | | |
| | 162 | 28 | 27.51 | 0.01 | 0.17 | 0.20 | 1 | 0.7000 |
| **10** $Epithelial^{low}$ mixed | 16 | 2 | 2.68 | 0.17 | 0.19 | | | |
| | 157 | 27 | 26.32 | 0.02 | 0.19 | 0.20 | 1 | 0.7000 |
| **11** $CK7^{+}$ | 19 | 0 | 3.47 | 3.47 | 3.97 | | | |
| | 154 | 29 | 25.53 | 0.47 | 3.97 | 4.00 | 1 | 0.0500 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 11 | 3 | 1.18 | 2.81 | 3.00 | | | |
| | 162 | 26 | 27.82 | 0.12 | 3.00 | 3.00 | 1 | 0.0800 |
| **13** Basal CK | 5 | 1 | 1.00 | 0.00 | 0.00 | | | |
| | 168 | 28 | 28.00 | 0.00 | 0.00 | 0.00 | 1 | 1.0000 |
| **14** Proliferative | 3 | 2 | 0.22 | 14.21 | 14.50 | | | |
| | 170 | 27 | 28.78 | 0.11 | 14.50 | 14.50 | 1 | 0.0001 |
| **15** $EGFR^{+}$ $p53^{+}$ | NA | NA | NA | NA | NA | | | |
| | NA | NA | NA | NA | NA | NA | NA | NA |
| **16** Apoptotic | 2 | 0 | 0.38 | 0.38 | 0.38 | | | |
| | 171 | 29 | 28.63 | 0.00 | 0.38 | 0.40 | 1 | 0.5000 |
| **17** Hypoxic | 3 | 2 | 0.32 | 8.75 | 8.90 | | | |
| | 170 | 27 | 28.68 | 0.10 | 8.90 | 8.90 | 1 | 0.0030 |
| **18** $CK^{-}$ $HR^{hi}p53^{+}$ *excluded* | *NA* | *NA* | *NA* | *NA* | *NA* | | | |
| | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |

**Supplementary Table 5**

**a)**

| **Single-Cell Pathology** | Coxph **Group vs All Others**, n = 278, number of events = 90 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | Nr. Patients | coef | exp(coef) | se(coef) | lower .95 | upper .95 | z | Pr(>\|z\|) |
| **1** $CK^{+}$ $Hr^{hi}$ | 17 | -0.28 | 0.75 | 0.46 | 0.31 | 1.86 | -0.61 | 0.5420 |
| **2** $CK^{+}$ $HR^{+}$ | 21 | 0.44 | 1.56 | 0.32 | 0.83 | 2.92 | 1.37 | 0.1700 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 20 | 0.16 | 1.17 | 0.35 | 0.59 | 2.34 | 0.45 | 0.6540 |
| 4 $CK^{+}$ $HR^{low}$ | 12 | 0.62 | 1.87 | 0.43 | 0.81 | 4.29 | 1.47 | 0.1430 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 32 | -1.10 | 0.33 | 0.46 | 0.14 | 0.83 | -2.38 | 0.0175 |
| **6** $CK^{low}$ $HR^{low}$ | 10 | 0.26 | 1.30 | 0.51 | 0.48 | 3.54 | 0.51 | 0.6090 |
| **7** $Epithelial^{low}$ | 13 | 0.31 | 1.37 | 0.42 | 0.60 | 3.13 | 0.74 | 0.4600 |
| **8** Mixed | 11 | 0.99 | 2.70 | 0.42 | 1.18 | 6.19 | 2.34 | 0.0192 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 20 | -0.20 | 0.82 | 0.46 | 0.33 | 2.02 | -0.44 | 0.6630 |
| **10** $Epithelial^{low}$ mixed | 24 | 0.22 | 1.25 | 0.35 | 0.63 | 2.48 | 0.63 | 0.5320 |
| **11** $CK7^{+}$ | 31 | -1.09 | 0.34 | 0.51 | 0.12 | 0.92 | -2.13 | 0.0329 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 14 | 0.45 | 1.58 | 0.46 | 0.64 | 3.91 | 0.98 | 0.3270 |
| **13** Basal CK | 15 | -0.12 | 0.88 | 0.51 | 0.32 | 2.41 | -0.24 | 0.8090 |
| **14** Proliferative | 11 | 0.65 | 1.92 | 0.46 | 0.78 | 4.74 | 1.41 | 0.1580 |
| **15** $EGFR^{+}$ $p53^{+}$ | 8 | -0.28 | 0.76 | 1.01 | 0.11 | 5.45 | -0.28 | 0.7830 |
| **16** Apoptotic | 10 | -1.21 | 0.30 | 1.01 | 0.04 | 2.14 | -1.20 | 0.2290 |
| **17** Hypoxic | 9 | 0.58 | 1.79 | 0.51 | 0.65 | 4.88 | 1.13 | 0.2580 |
| **18** $CK^{-}$ $HR^{hi}p53^{+}$ *excluded* | *3* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |

**b)**

| **Single-Cell Pathology** | Logrank **Group vs All Others** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V | Chisq | DF | P |
| **1** $CK^{+}$ $Hr^{hi}$ | 17 | 5 | 6.50 | 0.35 | 0.38 | | | |
| | 261 | 85 | 83.50 | 0.03 | 0.38 | 0.40 | 1 | 0.5000 |
| **2** $CK^{+}$ $HR^{+}$ | 21 | 11 | 7.41 | 1.74 | 1.91 | | | |
| | 257 | 79 | 82.59 | 0.16 | 1.91 | 1.90 | 1 | 0.2000 |
| **3** $CK^{+}$ $HR^{hi}$ & $CK^{low}$ $HR^{low}$ | 20 | 9 | 7.81 | 0.18 | 0.20 | | | |
| | 258 | 81 | 82.19 | 0.02 | 0.20 | 0.20 | 1 | 0.7000 |
| 4 $CK^{+}$ $HR^{low}$ | 12 | 6 | 3.35 | 2.09 | 2.21 | | | |
| | 266 | 84 | 86.65 | 0.08 | 2.21 | 2.20 | 1 | 0.1000 |
| **5** $CK^{+}$ $HR^{low}$ mixed | 32 | 5 | 13.40 | 5.24 | 6.25 | | | |
| | 246 | 85 | 76.60 | 0.91 | 6.25 | 6.30 | 1 | 0.0100 |
| **6** $CK^{low}$ $HR^{low}$ | 10 | 4 | 3.12 | 0.25 | 0.26 | | | |
| | 268 | 86 | 86.88 | 0.01 | 0.26 | 0.30 | 1 | 0.6000 |
| **7** $Epithelial^{low}$ | 13 | 6 | 4.47 | 0.53 | 0.56 | | | |
| | 265 | 84 | 85.53 | 0.03 | 0.56 | 0.60 | 1 | 0.5000 |
| **8** Mixed | 11 | 6 | 2.34 | 5.70 | 5.91 | | | |
| | 267 | 84 | 87.66 | 0.15 | 5.91 | 5.90 | 1 | 0.0200 |
| **9** $CK^{low}$ $HR^{low}$ mixed | 20 | 5 | 6.03 | 0.17 | 0.19 | | | |
| | 258 | 85 | 83.97 | 0.01 | 0.19 | 0.20 | 1 | 0.7000 |
| **10** $Epithelial^{low}$ mixed | 24 | 9 | 7.36 | 0.36 | 0.40 | | | |
| | 254 | 81 | 82.64 | 0.03 | 0.40 | 0.40 | 1 | 0.5000 |
| **11** $CK7^{+}$ | 31 | 4 | 10.90 | 4.38 | 5.02 | | | |
| | 247 | 86 | 79.10 | 0.60 | 5.02 | 5.00 | 1 | 0.0300 |
| **12** $CK7^{+}$ $CK^{hi}$ E/P-$Cadherin^{hi}$ | 14 | 5 | 3.27 | 0.91 | 0.96 | | | |
| | 264 | 85 | 86.73 | 0.03 | 0.96 | 1.00 | 1 | 0.3000 |
| **13** Basal CK | 15 | 4 | 4.50 | 0.05 | 0.06 | | | |
| | 263 | 86 | 85.50 | 0.00 | 0.06 | 0.10 | 1 | 0.8000 |
| **14** Proliferative | 11 | 5 | 2.69 | 1.98 | 2.06 | | | |
| | 267 | 85 | 87.31 | 0.06 | 2.06 | 2.10 | 1 | 0.2000 |
| **15** $EGFR^{+}$ $p53^{+}$ | 8 | 1 | 1.32 | 0.08 | 0.08 | | | |
| | 270 | 89 | 88.68 | 0.00 | 0.08 | 0.10 | 1 | 0.8000 |
| **16** Apoptotic | 10 | 1 | 3.26 | 1.57 | 1.65 | | | |
| | 268 | 89 | 86.74 | 0.06 | 1.65 | 1.60 | 1 | 0.2000 |
| **17** Hypoxic | 9 | 4 | 2.30 | 1.26 | 1.31 | | | |
| | 269 | 86 | 87.70 | 0.03 | 1.31 | 1.30 | 1 | 0.3000 |
| **18** $CK^{-}$ $HR^{hi}$ $p53^{+}$ *excluded* | *NA* | *NA* | *NA* | *NA* | *NA* | | | |
| | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* | *NA* |

**Supplementary Table 6**

**a)**

| **Stromal Environment** | Coxph **Group vs All Others**, n = 275, number of events = 56 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | Nr. Patients | coef | exp(coef) | se(coef) | lower .95 | upper .95 | z | Pr(>\|z\|) |
| **1** | 49 | -0.28 | 0.76 | 0.37 | 0.37 | 1.55 | -0.76 | 0.4490 |
| **2** | 88 | -0.15 | 0.86 | 0.29 | 0.49 | 1.52 | -0.51 | 0.6070 |
| **3** | 9 | 0.74 | 2.09 | 0.59 | 0.65 | 6.69 | 1.24 | 0.2160 |
| **4** | 24 | 0.38 | 1.47 | 0.43 | 0.63 | 3.43 | 0.89 | 0.3750 |
| **5** | 25 | -0.97 | 0.38 | 0.72 | 0.09 | 1.56 | -1.34 | 0.1800 |
| **6** | 24 | 0.64 | 1.90 | 0.36 | 0.93 | 3.87 | 1.75 | 0.0795 |
| **7** | 8 | 0.26 | 1.30 | 0.72 | 0.32 | 5.35 | 0.37 | 0.7140 |
| **8** | 14 | 0.43 | 1.53 | 0.59 | 0.48 | 4.91 | 0.72 | 0.4740 |
| **9** | 14 | -0.24 | 0.79 | 0.72 | 0.19 | 3.24 | -0.33 | 0.7410 |
| **10** | 18 | -0.34 | 0.71 | 0.72 | 0.17 | 2.93 | -0.47 | 0.6370 |
| **11** | 2 | -15.01 | 0.00 | 3528.00 | 0.00 | Inf | 0.00 | NA |

**b)**

| **Stromal Environment** | Logrank **Group vs All Others** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V | Chisq | DF | P |
| **1** | 49 | 9 | 11.30 | 0.45 | 0.57 | | | |
| | 226 | 47 | 44.70 | 0.11 | 0.57 | 0.60 | 1 | 0.4000 |
| **2** | 88 | 18 | 36.20 | 0.09 | 0.27 | | | |
| | 187 | 38 | 36.20 | 0.09 | 0.27 | 0.30 | 1 | 0.6000 |
| **3** | 9 | 3 | 1.48 | 1.56 | 1.61 | | | |
| | 266 | 53 | 54.52 | 0.04 | 1.61 | 1.60 | 1 | 0.2000 |
| **4** | 24 | 6 | 4.24 | 0.74 | 0.80 | | | |
| | 251 | 50 | 51.76 | 0.06 | 0.80 | 0.80 | 1 | 0.4000 |
| **5** | 25 | 2 | 4.94 | 1.75 | 1.93 | | | |
| | 250 | 54 | 51.06 | 0.17 | 1.93 | 1.90 | 1 | 0.2000 |
| **6** | 24 | 9 | 5.16 | 2.85 | 3.16 | | | |
| | 251 | 47 | 50.84 | 0.29 | 3.16 | 3.20 | 1 | 0.0800 |
| **7** | 8 | 2 | 1.56 | 0.13 | 0.13 | | | |
| | 267 | 54 | 54.44 | 0.00 | 0.13 | 0.10 | 1 | 0.7000 |
| **8** | 14 | 3 | 2.00 | 0.50 | 0.52 | | | |
| | 261 | 53 | 54.00 | 0.02 | 0.52 | 0.50 | 1 | 0.5000 |
| **9** | 14 | 2 | 2.51 | 0.10 | 0.11 | | | |
| | 261 | 54 | 53.49 | 0.00 | 0.11 | 0.10 | 1 | 0.7000 |
| **10** | 18 | 2 | 2.76 | 0.21 | 0.22 | | | |
| | 257 | 54 | 53.24 | 0.01 | 0.22 | 0.20 | 1 | 0.6000 |
| **11** | 2 | 0 | 0.26 | 0.26 | 0.27 | | | |
| | 273 | 56 | 55.74 | 0.00 | 0.27 | 0.30 | 1 | 0.6000 |

**Supplementary Table 7**

**a)**

| **Stromal Environment** | Coxph **Group vs All Others**, n = 275, number of events = 89 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | Nr. Patients | coef | exp(coef) | se(coef) | lower .95 | upper .95 | z | Pr(>\|z\|) |
| **1** | 49 | -0.25 | 0.78 | 0.29 | 0.44 | 1.37 | -0.87 | 0.3820 |
| **2** | 88 | -0.22 | 0.80 | 0.23 | 0.51 | 1.26 | -0.97 | 0.3330 |
| **3** | 9 | 0.57 | 1.77 | 0.51 | 0.65 | 4.84 | 1.12 | 0.2650 |
| **4** | 24 | -0.01 | 0.99 | 0.39 | 0.46 | 2.14 | -0.03 | 0.9730 |
| **5** | 25 | -0.56 | 0.57 | 0.46 | 0.23 | 1.41 | -1.22 | 0.2230 |
| **6** | 24 | 0.81 | 2.26 | 0.28 | 1.30 | 3.93 | 2.87 | 0.0041 |
| **7** | 8 | 0.13 | 1.14 | 0.59 | 0.36 | 3.60 | 0.22 | 0.8260 |
| **8** | 14 | -0.16 | 0.85 | 0.59 | 0.27 | 2.71 | 0.27 | 0.7890 |
| **9** | 14 | -0.36 | 0.70 | 0.59 | 0.22 | 2.21 | -0.61 | 0.5390 |
| **10** | 18 | 0.42 | 1.52 | 0.39 | 0.70 | 3.29 | 1.06 | 0.2900 |
| **11** | 2 | 2.28 | 9.73 | 1.02 | 1.31 | 72.44 | 2.22 | 0.0263 |

**b)**

| **Stromal Environment** | Logrank **Group vs All Others** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient Group** | N | Observed | Expected | (O-E)^2/E | (O-E)^2/V | Chisq | DF | P |
| **1** | 49 | 14 | 17.20 | 0.61 | 0.76 | | | |
| | 226 | 75 | 71.80 | 0.15 | 0.76 | 0.80 | 1 | 0.4000 |
| **2** | 88 | 27 | 31.40 | 0.60 | 0.94 | | | |
| | 187 | 62 | 57.60 | 0.33 | 0.94 | 0.90 | 1 | 0.3000 |
| **3** | 9 | 4 | 2.32 | 1.22 | 1.27 | | | |
| | 266 | 85 | 86.68 | 0.03 | 1.27 | 1.30 | 1 | 0.3000 |
| **4** | 24 | 7 | 7.10 | 0.00 | 0.00 | | | |
| | 251 | 82 | 81.90 | 0.00 | 0.00 | 0.00 | 1 | 1.0000 |
| **5** | 25 | 5 | 8.38 | 1.37 | 1.52 | | | |
| | 250 | 84 | 80.62 | 0.14 | 1.52 | 1.50 | 1 | 0.2000 |
| **6** | 24 | 15 | 7.35 | 7.96 | 8.74 | | | |
| | 251 | 74 | 81.65 | 0.72 | 8.74 | 8.70 | 1 | 0.0030 |
| **7** | 8 | 3 | 2.66 | 0.04 | 0.04 | | | |
| | 267 | 86 | 86.34 | 0.00 | 0.04 | 0.00 | 1 | 0.8000 |
| **8** | 14 | 3 | 3.49 | 0.07 | 0.07 | | | |
| | 261 | 86 | 85.51 | 0.00 | 0.07 | 0.10 | 1 | 0.8000 |
| **9** | 14 | 3 | 4.23 | 0.36 | 0.38 | | | |
| | 261 | 86 | 84.77 | 0.02 | 0.38 | 0.40 | 1 | 0.5000 |
| **10** | 18 | 7 | 4.76 | 1.05 | 1.12 | | | |
| | 257 | 82 | 84.24 | 0.06 | 1.12 | 1.80 | 1 | 0.2000 |
| **11** | 2 | 1 | 0.11 | 6.95 | 7.05 | | | |
| | 273 | 88 | 88.89 | 0.09 | 7.05 | 7.00 | 1 | 0.0080 |

**Supplementary Table 8**

| **Likelihood Ratio Tests** | Coxph models | loglik | Chisq | DF | P(>\|Chi\|) |
|---|---|---|---|---|---|
| Model 1 | Clinical Subgroups | -267.30 | | | |
| Model 2 | Clinical Subgroups + Community Densities | -224.19 | 86.21 | 53.00 | 0.0026 |
| Model 1 | Clinical Subgroups + Grades | -260.20 | | | |
| Model 2 | Clinical Subgroups + Grades + Community Densities | -216.87 | 86.66 | 53.00 | 0.0024 |
| Model 1 | Grades | -262.85 | | | |
| Model 2 | Grades + Community Densities | -230.03 | 65.64 | 53.00 | 0.1140 |
| Model 1 | Grades | -262.85 | | | |
| Model 2 | Grades + Clinical Subgroups | -260.20 | 5.30 | 4.00 | 0.2576 |
| Model 1 | Clinical Subgroups | -284.31 | | | |
| Model 2 | Clinical Subgroups + Single-Cell Densities | -266.62 | 35.38 | 27.00 | 0.1295 |
| Model 1 | Clinical Subgroups + Grade | -278.78 | | | |
| Model 2 | Clinical Subgroups + Grade + Single-Cell Densities | -259.80 | 37.95 | 27.00 | 0.0787 |
| Model 1 | Clinical Subgroups | -278.37 | | | |
| Model 2 | Clinical Subgroups + SCP Groups | -260.36 | 36.02 | 16.00 | 0.0029 |
| Model 1 | Clinical Subgroups + Grade | -272.54 | | | |
| Model 2 | Clinical Subgroups + Grade + SCP Groups | -256.76 | 31.56 | 16.00 | 0.0114 |

**Supplementary Table 9**

| Metadata | Values | Patient Counts/ Means |
|---|---|---|
| Grade | 1 | 19 |
| | 2 | 26 |
| | 3 | 27 |
| Tumor Size [mm] | 8 - 80 | 26.93 |
| Age [years] | 42 - 60 | 53.77 |
| Gender | Female | 72 |
| | Male | 0 |
| Menpausal | Pre | 0 |
| | Post | 72 |
| PTNM_M | 0 | 31 |
| | 0 plus | 2 |
| | 1 | 39 |
| PTNM_T | 1a | 1 |
| | 1b | 4 |
| | 1c | 27 |
| | 2 | 27 |
| | 3 | 9 |
| | 4 | 1 |
| PTNM_N | 0 | 23 |
| | 1 | 11 |
| | 1mi | 4 |
| | 1a | 11 |
| | 2 | 1 |
| | 2a | 3 |
| | 3a | 3 |
| ER Status | Positive | 51 |
| | Negative | 21 |
| PR Status | Positive | 43 |
| | Negative | 29 |
| HER2 Status | Positive | 14 |
| | Negative | 58 |
| Clinical Subtype | HR+HER2+ | 12 |
| | HR+HER2- | 39 |
| | HR-HER2+ | 2 |
| | TripleNeg | 9 |