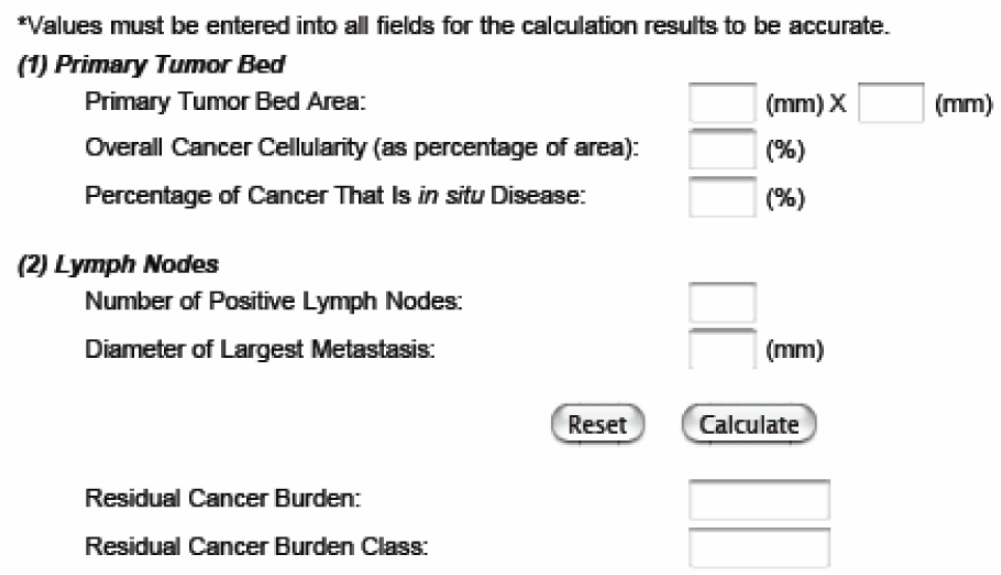
Detailed Pathology Methods for Using Residual Cancer Burden

Residual cancer burden (RCB) is estimated from routine pathologic sections of the primary breast tumor site and the regional lymph nodes after the completion of neoadjuvant therapy. Six variables are included in a calculation formula. The calculated RCB index value can also be categorized as one of four RCB classes. The calculation formula and detailed description can be found at a dedicated Web site: http://www.mdanderson.org/breastcancer_RCB.



Relevant information can be included within a pathology report (diagnoses or comment) without need for reporting calculated RCB index results. An example of relevant information from a report would be:

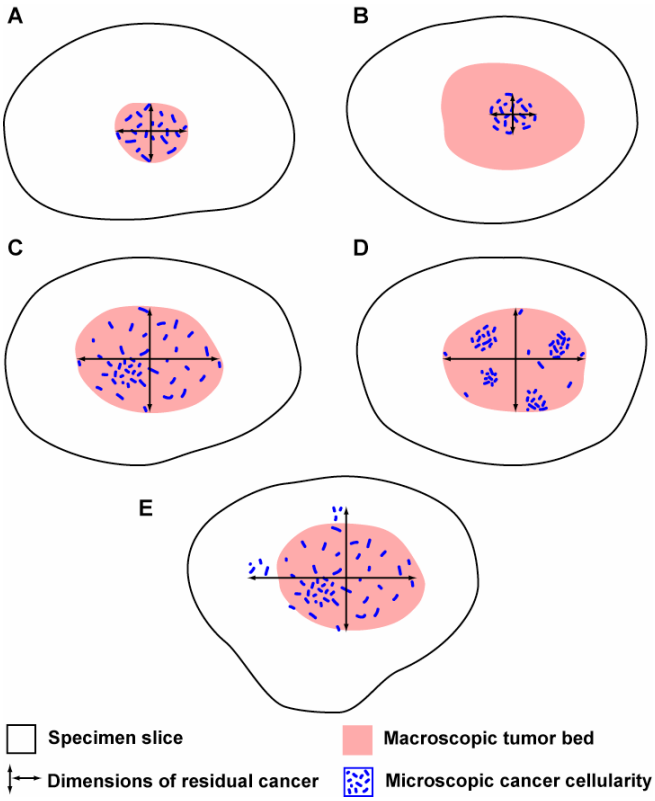
- Residual invasive carcinoma with chemotherapy effect
- Residual carcinoma measures 2.4 x 1.8 cm and contains approximately 10% cancer cellularity
- Residual intraductal carcinoma, solid type with necrosis, comprising 5% of the residual carcinoma
- Metastatic carcinoma involving three of 14 axillary lymph nodes (3/14)
- The largest metastasis measures 4 mm in greatest dimension

From the results above, one could calculate RCB using these results: d_1 = 24 mm, d_2 = 18 mm, *%CA* = 10%, *%CIS* = 5%, *LN* = 3, d_{met} = 4 mm.

Primary Tumor Bed: In general terms, pathologic evaluation of the primary tumor bed in the breast requires that the pathologist make three judgments about the primary tumor bed:

i. Identify the cross-sectional dimensions of the residual tumor bed (d_1 and d_2),
ii. Estimate of the proportion of that residual tumor bed area that is involved by cancer (*%CA*), and
iii. Estimate the proportion of the cancer that is *in situ* component (*%CIS*).

Defining the Tumor Bed.
In cases of multicentric disease, the RCB measurements are from the largest residual tumor bed. In cases where the extent of residual cancer under the microscope does not correlate with the gross measurement of the residual tumor bed, the tumor bed dimensions are to be revised according to the microscopic findings. Schematic diagrams are shown below to illustrate how gross residual tumor bed dimensions are first estimated from the gross findings (pink area) but may be revised after review of the slides from the gross tumor bed area according to the extent of residual cancer (blue).



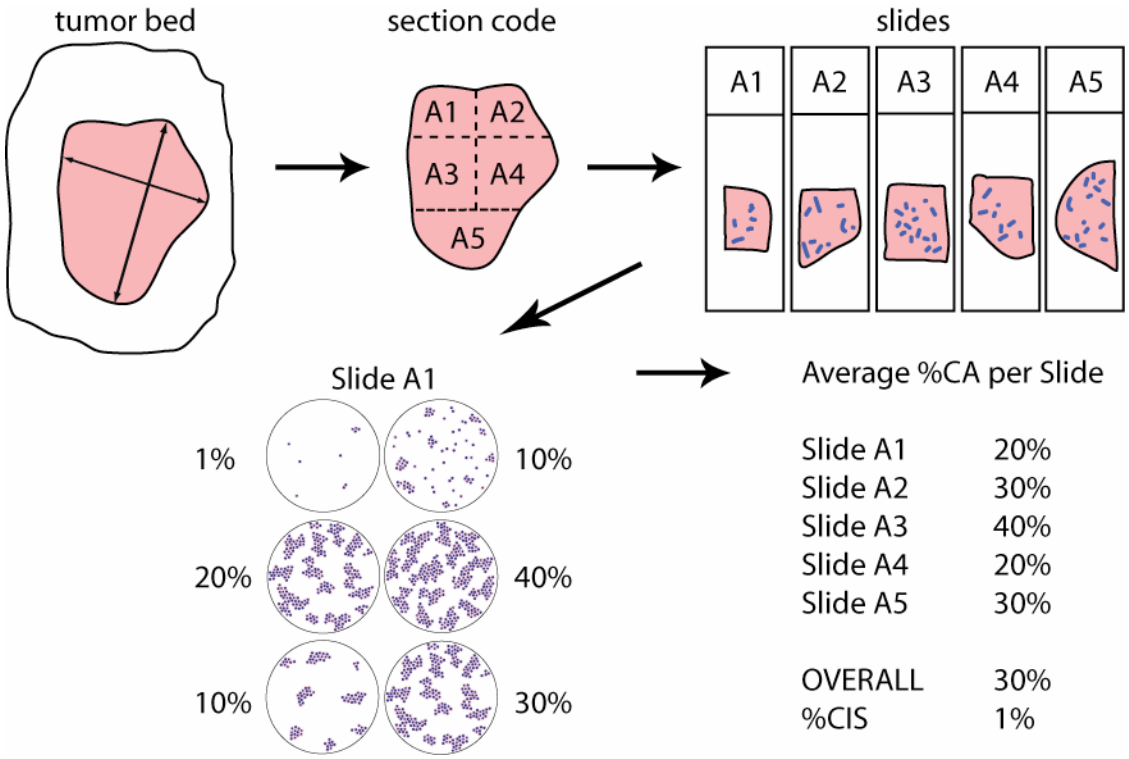
In these diagrams, the macroscopic tumor bed dimensions in examples A, C, D also define the final dimensions of the residual tumor bed after microscopic review. However, the macroscopic tumor bed dimensions in example B overestimate the extent of residual cancer, and so the dimensions of the residual tumor bed (d_1 and d_2) would be revised after microscopic evaluation of the extent of residual cancer in the corresponding slides from the gross tumor bed. In a different example (E), microscopic residual cancer extends beyond the confines of the macroscopic tumor bed. Again, the dimensions of the residual tumor bed (d_1 and d_2) would be revised after microscopic evaluation of the recognizable extent of residual cancer beyond the macroscopic tumor bed.

This approach accounts for differences in the concentration and distribution of residual cancer within a tumor bed. In the illustration above, the estimated *%CA* in example A would be high (in a small area), whereas the estimated *%CA* for examples C and D would be lower (in a larger area). In examples C and D, the estimated *%CA* would likely be similar, even though the distribution of cancer within the residual tumor bed is different in those two examples.

Estimating Cellularity within the Tumor Bed
The proportion of cancer (*%CA*) and the proportion of *in situ* component (*%CIS*) are estimated from microscopic evaluation of the slides from the residual tumor bed area. The most effective way to obtain this information is to measure and submit for histology the largest cross-sectional area of residual tumor bed, and to designate in the report which slides represent the cross section of tumor bed. After reviewing those slides, the pathologist can estimate the average cellularity in the tumor bed on each slide in order to estimate the overall average cellularity of the tumor bed area (illustrated below).

The key is to simply:

i. Define the gross tumor bed as the largest cross-sectional area.
ii. Submit sections representing that tumor bed area as individual slides.
iii. Review those slides to estimate the *%CA* and *%CIS* within the residual tumor bed.



A practical way to estimate %CA in a slide is to encircle with ink dots the tumor bed on each slide from the grossly defined residual tumor bed (e.g., slides A1-A5 in the example above). Then use the microscope to estimate the cellularity in each microscopic field across the area of tumor bed. In each microscopic field, *%CA* can be estimated by comparing the proportion of residual tumor bed area containing cancer (invasive or *in situ*). Estimate an average of the readings for *%CA* in the cross-sectional area. The same can be done for *in situ* component (*%CIS*). Estimates are to the nearest 10%, but include 0%, 1%, and 5% for areas with low cellularity. The average cellularity within the tumor bed from each slide across the tumor bed can then be estimated (illustrated above). The website contains computer-generated diagrams of % cellularity per area to assist pathologists to estimate accurately the cellularity of a microscopic field. Those diagrams are appended at the end of this document.

Regional Lymph Nodes: Pathologic evaluation of the primary tumor bed in the breast requires that the pathologist make two judgments:

i. Count the number of positive lymph nodes (*LN*).
ii. Measure the diameter of the largest nodal metastasis (d_{met}).

Footnotes

Inoperable or Progressive Disease

The RCB index cannot be accurately calculated for patients whose disease remains inoperable at the completion of the neoadjuvant treatment course (e.g., requiring subsequent additional treatments before surgical resection is possible), or those who experience disease progression and so do not undergo surgical resection at the completion of the neoadjuvant treatment course. For those patients, RCB is assigned as extensive, i.e., RCB-III.

Internal Mammary Lymph Node Metastasis

There were no examples of internal mammary nodal metastasis in the published study that evaluated the prognostic value of RCB. However, it is reasonable to include internal mammary nodes with the other regional (axillary) nodes in the assessment of RCB.

Pre-treatment Sentinel Lymph Node Biopsy

Surgical excision of a positive sentinel lymph node before the neoadjuvant treatment would invalidate the accuracy of measuring RCB after the treatment to assess response. If all sentinel lymph nodes were negative before treatment began, this would not affect the assessment of RCB after treatment ended.

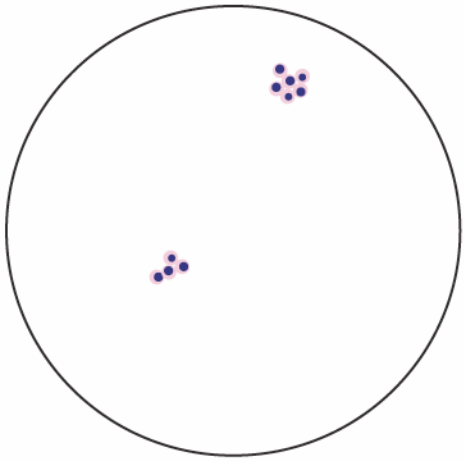
Summary of Key Points for Pathologic Assessment of the Primary Tumor Bed

Define the dimensions of residual tumor bed and estimate the percent of that area that is cancer.

1. **GROSS**. Identify the probable tumor bed and describe this macroscopic finding:
    a. Report the measurements of the largest gross dimensions (prefer three dimensions, but minimum is two dimensions).
    b. Submit the largest cross-sectional area for histology and specifically describe those blocks in the Section Code:
        i. Try to indicate how they are oriented by photography, radiography, photocopy, or intelligent description (e.g., “sections B1 – B7 cross section of tumor bed in rows from antero-superior to postero-inferior”).
        ii. If additional sections are from surrounding tissues, then describe those as well.
        iii. Five representative sections from a big, obvious tumor bed should be sufficient.

2. **MICROSCOPY**. Review the slides that correspond to the tumor bed (+/- surrounding tissues):
    a. Estimate the extent of spread of residual cancer relative to the gross tumor bed:
        i. If similar to the gross description, then keep the original measurements.
        ii. If obviously different, then revise the dimensions of the tumor bed based on the microscopic review of the tumor bed.
        iii. Suggestion: Dotting the perimeter of cancer in each slide can be helpful to reconstruct the tumor extent across multiple slides (see point 1-b-i).
    b. Using the microscope, make visual snapshots of cancer cellularity as you go from field to field across the defined tumor bed from one end to the opposite (e.g., left to right, then top to bottom) to estimate the:
        i. Average cancer cellularity (%) across the entire tumor bed. This is all cancer, whether invasive or *in situ*.
        ii. Average percent of the cancer within the tumor bed that is *in situ*.
        iii. Cellularity estimates are to the nearest 10%, with additional selections of 1% and 5% for very low cellularity. For reference, there are images of computer-generated examples linked to our Web site: http://www.mdanderson.org/breastcancer_RCB.
        iv. The usual misunderstanding is to only make estimates in foci of the tumor bed that contain lots of cancer. *The estimates are supposed to represent the average across the entire residual tumor bed area.*

Graphical Illustrations of Percentage Cancer Cellularity



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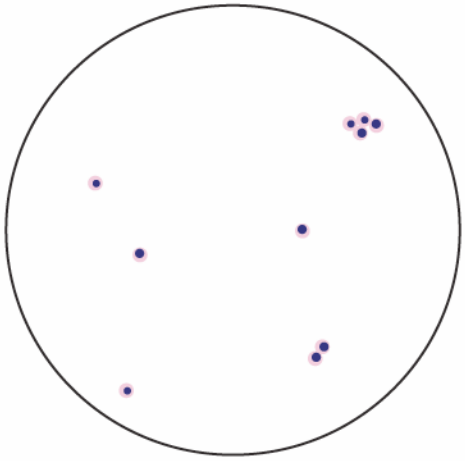

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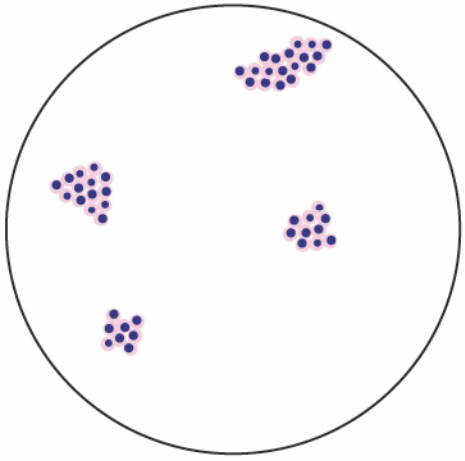

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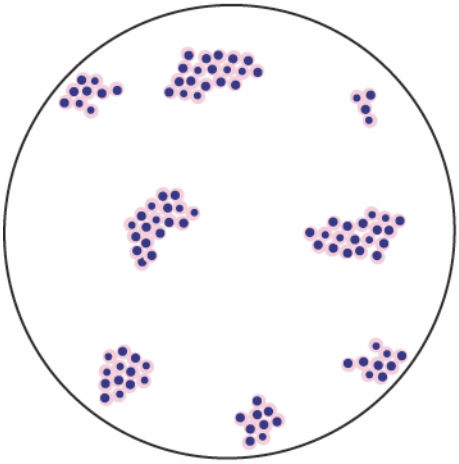

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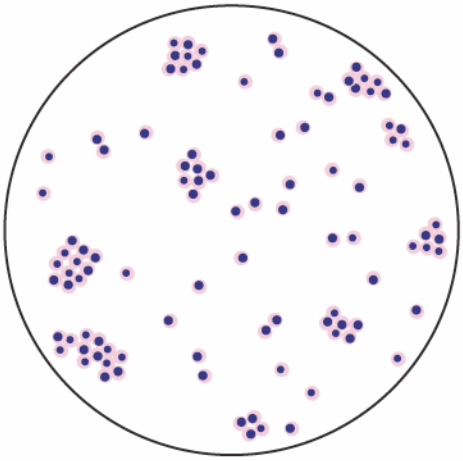

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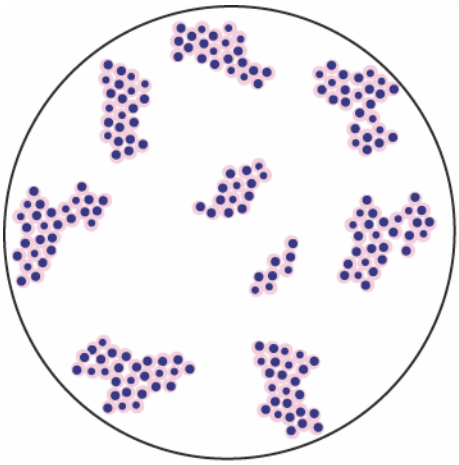

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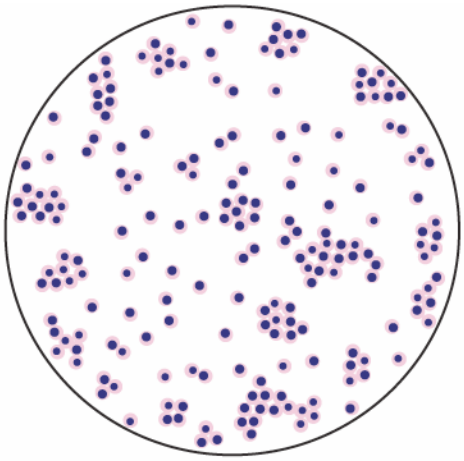

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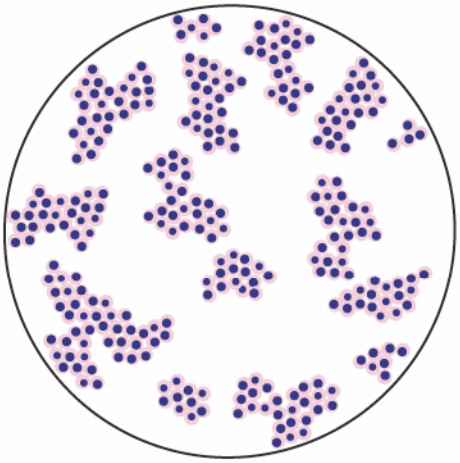

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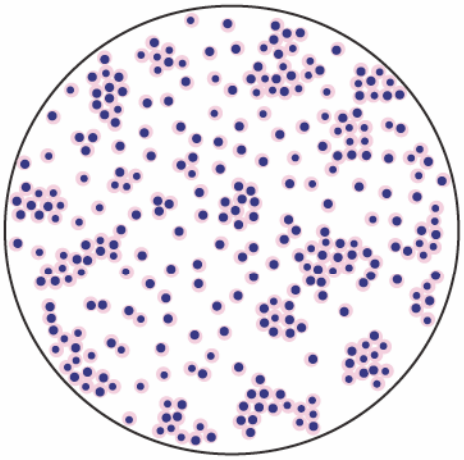

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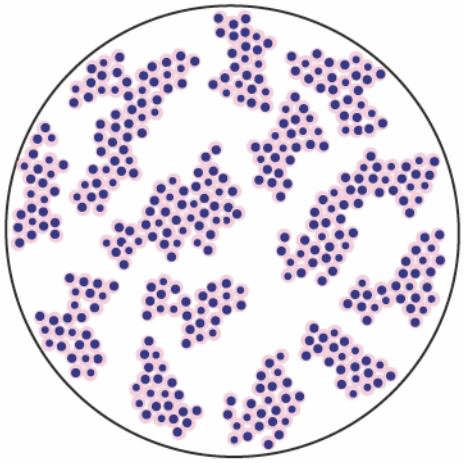

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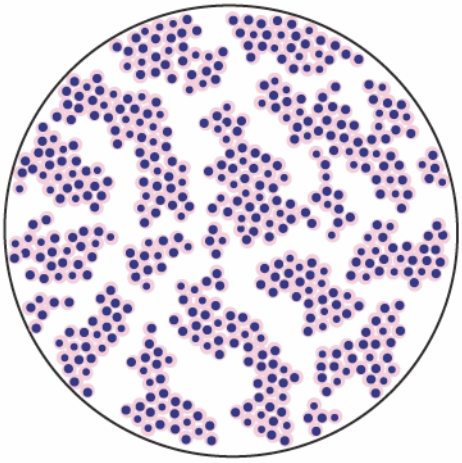

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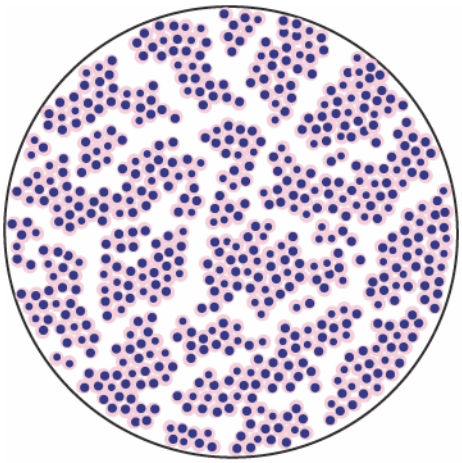

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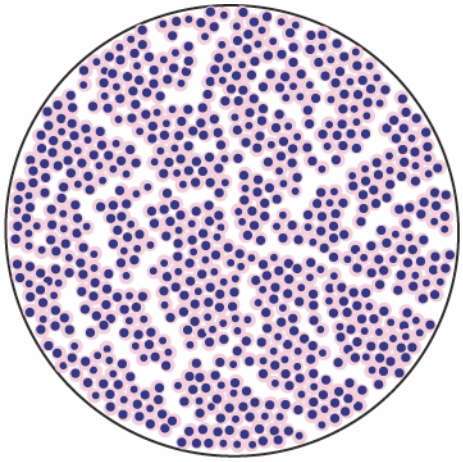

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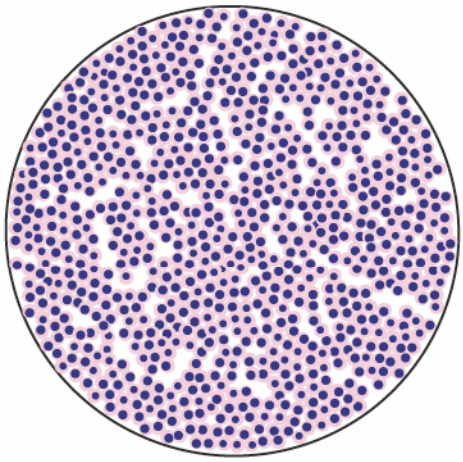

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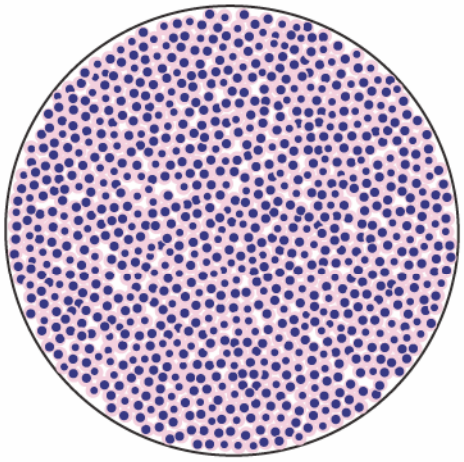

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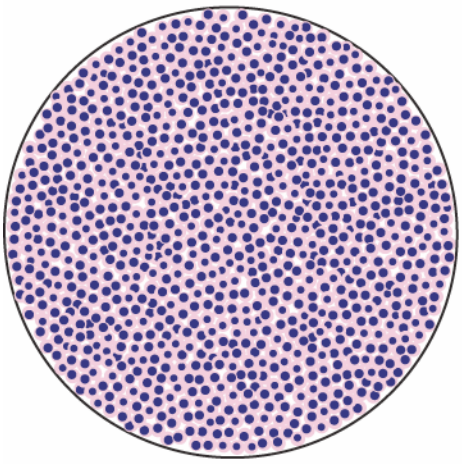

95%

DETAILS OF THIS MODEL

Area of circle = 2,827.8 mm^2

Area of 1 cell = 2.8278 mm^2

1 cell = 0.1% of Area = 0.1% cellularity

10 cells = 1% cellularity

1000 cells = 100% cellularity