Screening for bone marrow cellularity changes in cynomolgus macaques in toxicology safety studies using artificial intelligence models

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BACKGROUND

Bone marrow cellularity is the volume ratio of hematopoiesis and fat. Xenobiotics can affect the cellularity of bone marrow making it a vital tissue for analysis by pathologists in pharmacologic safety studies.

STUDY DESIGN

An AI model was trained to differentiate hematopoietic cells from other sternebrae tissues with the goal of serving as an objective measure of bone marrow cellularity in tissue sections.

Image Analysis Software and CNN Training

- 26 hematoxylin and eosin (H&E) stained whole slide images (WSI) of sternebrae from cynomolgus macaques

Training:

- 6 sections of sternum used as control
- 1 pathologist and 1 software scientist (1-2 weeks)
- 198 annotation regions
- 690 hematopoetic cells

Validation and Application:

- 20 sections of sternum selected from an independent study in which cellularity was determined by a pathologist
  - 10 used for validation
- 4 anatomic pathologists and 1 clinical pathologist

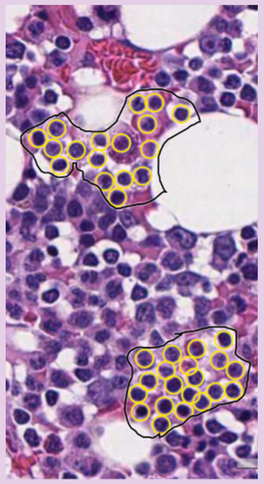
WORKFLOW

Training

Training annotations
Defined training areas and annotated within the training area

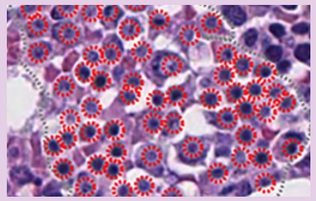
Defined layers

1. Bone and marrow space
2. Segmented marrow from cortical and trabecular bone
3. Hematopoietic cells, excluding fat and blood vessels
4. Object counter for a total of 690 annotated hematopoietic cells

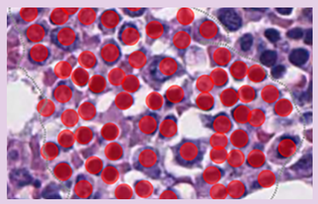


Cell count annotations

Validation



Pathologist annotated hematopoietic cells (dashed red circles)



Hematopoietic cells annotated by the AI model (solid red circles)

Define Regions of Interest (ROI)

- 10 WSIs representing cellularity variety
- 30 ROIs (3 per slide)
- ROIs represent different appearances/ cellularities

Define Validators
Comparison of the AI model and a team of veterinary pathologists

- 1 Clinical Pathologist
- 4 Anatomic Pathologists
- Provide standardized validation training

Application

Deploy the AI model to new images

- 20 animals selected
- Deploy the AI model
- Determine cell density of original data and compare to pathologist scores

AI model annotations of Layer 3: Bone marrow space excluding adipocytes

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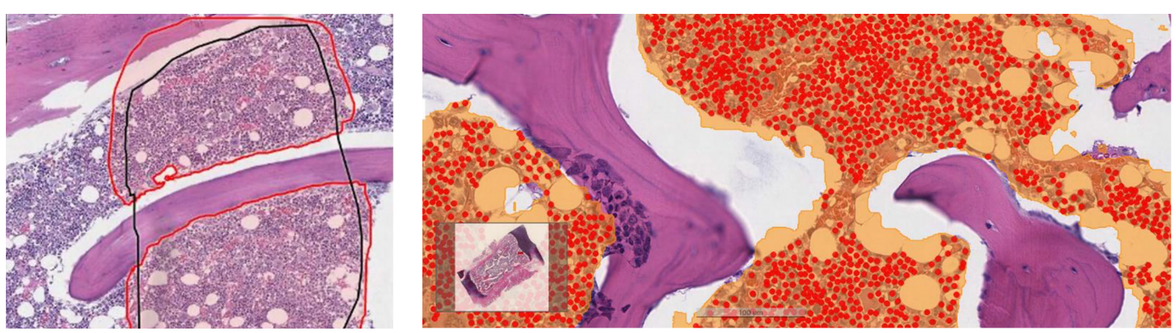
RESULTS

- AI model can recognize and count cells in the bone marrow and cell counts are comparable to pathologists cell counts.
- AI model can be used as a screening tool to alert pathologists of cellularity changes (decision support)
- AI model can be trained with limited resources (1 pathologist)



Training annotations (left) and application of AI model (right) of Layer 2: Tissue (bone marrow compartment)