Using Deep Learning Artificial Intelligence (AI) Algorithms to Verify N-nitroso-N-methylurea (NMU) and Urethane Positive Control Proliferative Changes in Tg-rasH2 Mouse Carcinogenicity Studies.

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Deep Learning enables screening for tumor positive and negative Tg-RasH2 mice in positive control groups at 100% concordance with toxicologic pathologists.

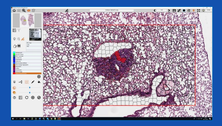
INTRODUCTION

- Preclinical carcinogenicity studies require considerable pathology effort and involving the evaluation of 10000 to 30000 or more tissues
- Large proportion of these being normal or having only background changes.
- The Tg-rasH2 mouse, model uses a positive control group treated with a known carcinogen such as urethane or N-nitroso-N-methylurea (NMU).

METHODS

- Training & testing sets- 20x whole slide scans (WSS) of serial sectioned H&E stained lungs, thymus, and stomach
- Supervised training of a convolutional neural network (CNN) using Patholytix Preclinical
- Trainer (ACVP board certified pathologist) verification and retraining
- Testing with separate pathology group using unique digital scan set

Annotate

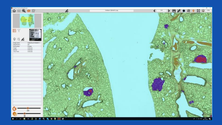


Annotate regions of example lesions
Annotate background and false positive

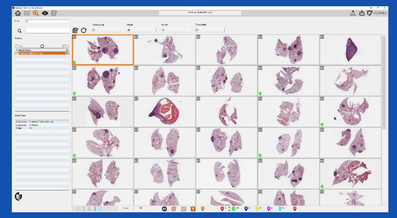
Train

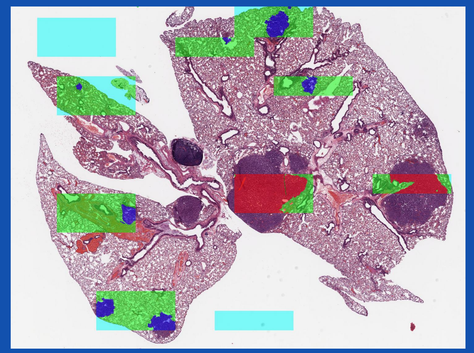
Train a variety of models
With training data provided

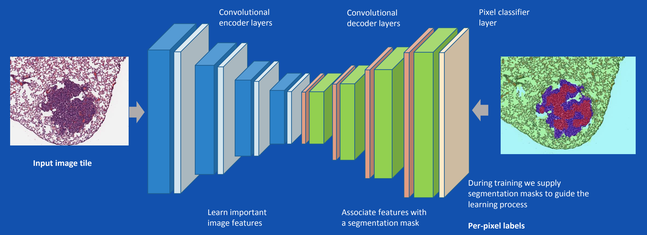
Deploy



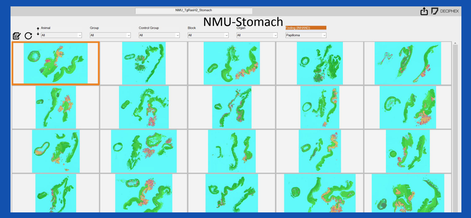
Use Model to Deploy Slide Image
Masks that Overlay on Images



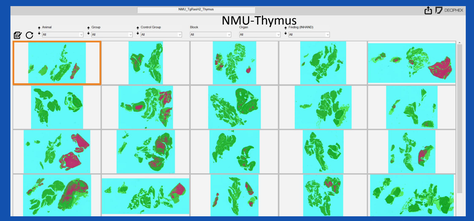




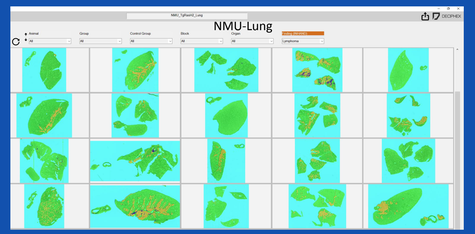
Hypothesis: Deep Learning-based algorithms can effectively screen for proliferative lesions in Tg-RasH2 mice



Red= Papilloma; Yellow= Hyperplasia



Red= Lymphoma



Yellow= Lymphoma

Placeholder for Urethane-Lung

RESULTS

- **Training using 15 cases and <75 annotations sufficient for all three tissues**
- **Algorithm tuned for high sensitivity (error towards falsae positives)**
- **Key endpoint= Tumor Positive or Tumor Negative at 100% concordance with testing group**
- **Workflow optimized to allow for visual (heat map presentation) for efficient diagnostic support for pathologist**
- **Decison to verify the positive control group could be made in minutes (versus days) without the need for data entry and revioew of non essential tissues**

CONCLUSIONS

- The DL-CNN algorithm provided efficient decision support for the pathologist
- The algorithm design supported high sensitivity for the intended use
- The workflow using the DL-CNN support tool would save approximately 3 working days of specialist (pathologist) effort per study
- The DL-CNN support tool could be extended to other tissues for tumor screening

Challenges and Next Steps:

- Cross site study of the DL-CNN algorithm
- Incorporation tool into CRL Tg-RasH2 study workflow
- Test DL-CNN as a "computer" scientific review tool

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