Erasmus MC
University Medical Center Rotterdam

Cancer Institute

# *"Mutation stratification of desmoid-type fibromatosis using a radiomics approach – preliminary results"*

DTRF 2018


**Milea J.M. Timbergen[1,2]*, MD, PhD candidate**

**Department of Surgical Oncology, Department of Medical Oncology**

**Martijn P.A. Starmans[3,4], Msc, PhD candidate**

**Department of Medical Informatics, Department of Radiology**

Melissa Vos, [1,2] Guillaume A. Padmos[4], Dirk J. Grünhagen[1], Geert H.J. van Leenders[5], Cornelis Verhoef[1], Wiro J. Niessen[3,4,6], Stefan Sleijfer[2], Stefan Klein[3,4] Jacob J. Visser[4]

[1] Department of Surgical Oncology, Erasmus MC Cancer Institute Rotterdam, the Netherlands

[2] Department of Medical Oncology, Erasmus MC Cancer Institute Rotterdam, the Netherlands

[3] Department of Medical Informatics, Erasmus MC, Rotterdam, the Netherlands

[4] Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

[5]Department of Pathology, Erasmus MC, Rotterdam, the Netherlands

[6]Faculty of Applied Sciences, Delft University of Technology, the Netherlands

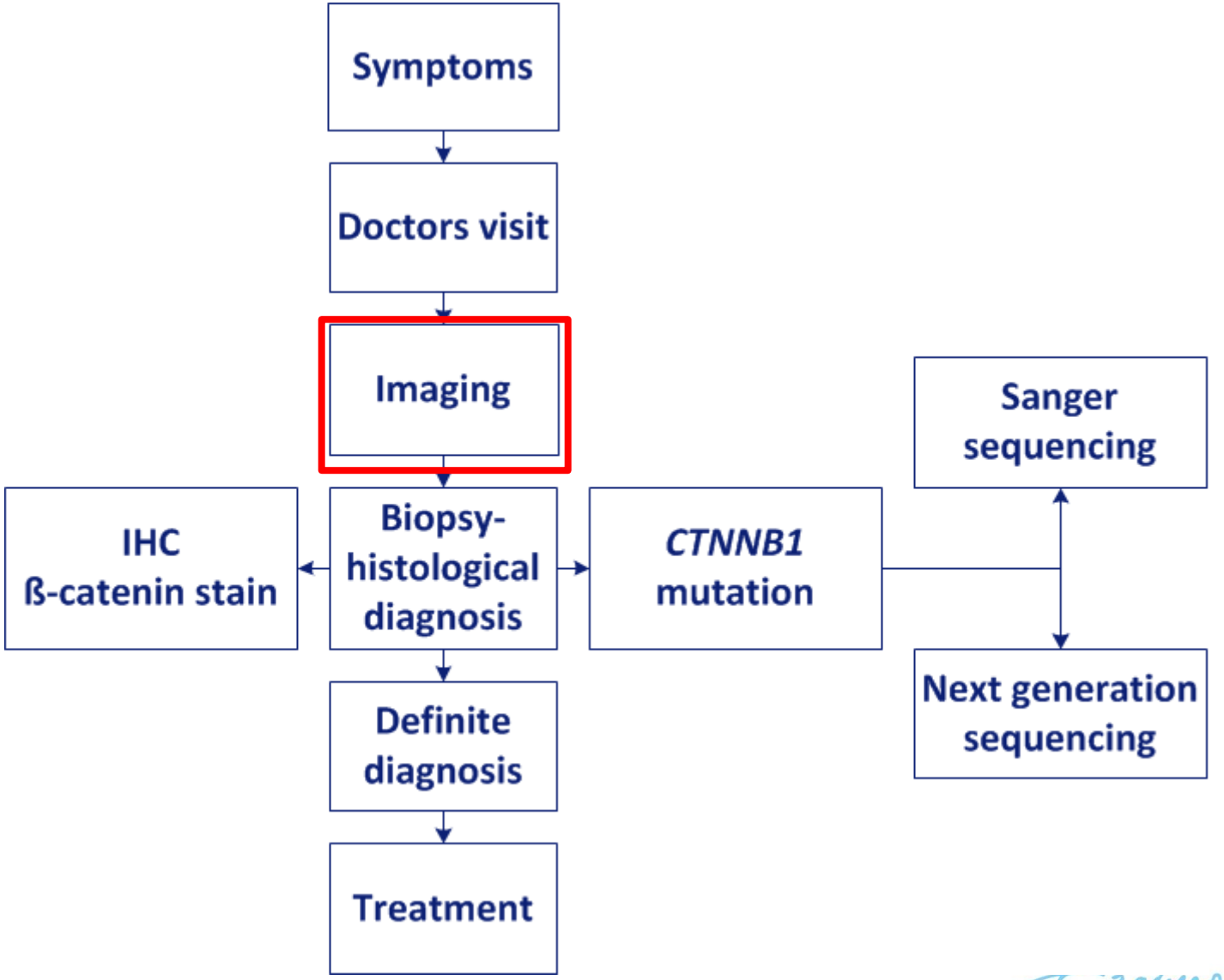
## Disclosure

Non-profit organisation

## The vast majority of desmoid tumors harbor a *CTNNB1* mutation

- About 80-90% of DTF tumors harbor a mutation in the *CTNNB1* (ß-catenin) gene[1]
- Supportive diagnostic tool
- Prognostic value?
  - S45F *CTNNB1* mutations have higher recurrence rates[2-5]

# The traditional diagnostic pathway of DTF



## Radiomics – make use of conventional imaging methods

- Identification of imaging features that serve as molecular surrogates
- Non-invasive method
- Widely available (pre-treatment) images
- 3D (multiple planes)

# Radiomics – previous studies

## Non-small cell lung cancer[6]

**Gevaert et al. 2017**

- Prediction of epidermal growth factor receptor (EGFR) mutation status
- n=186, CT imaging
- 16 semantic features significantly correlated with presence of EGFR (e.g. emphysema, distribution, nodules)
- **AUC value 0.89**

## Clear-cell renal cell carcinoma[7]

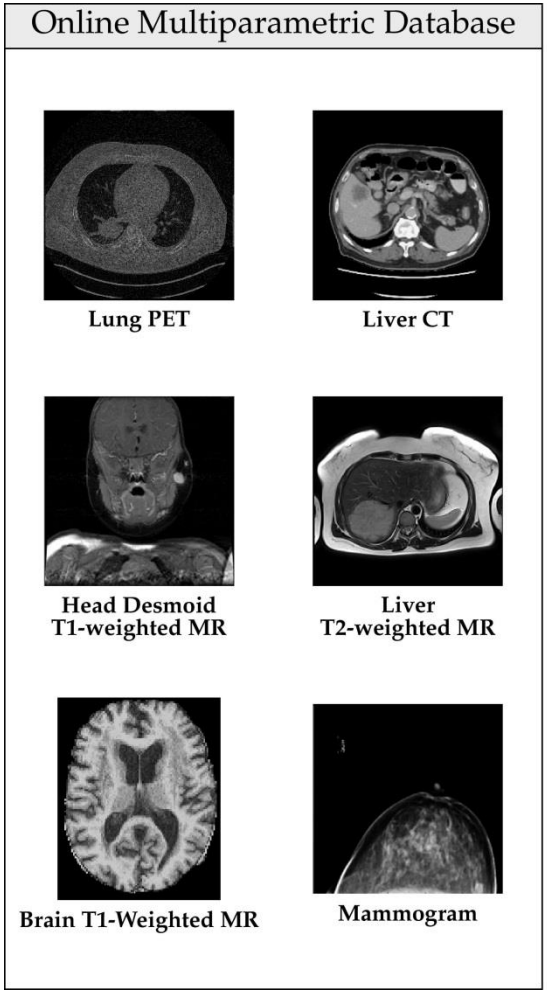
**Karlo et al. 2014**

- CT features and mutation status (VHL, PBRM1, SETD2, KDM5C, BAP1 genes)
- n=233, CT imaging
- VHL gene:**well defined tumor margins** (p=0.013), **nodular tumor enhacement** (p=0.021) and **gross appearance of intratumoral vascularity** (p=0.018)
- KDM5C and BAP1: **renal vein invasion** (p=0.022) and (p=0.046) resp

## Can we use radiomics in the clinical practice in the context of DTF?

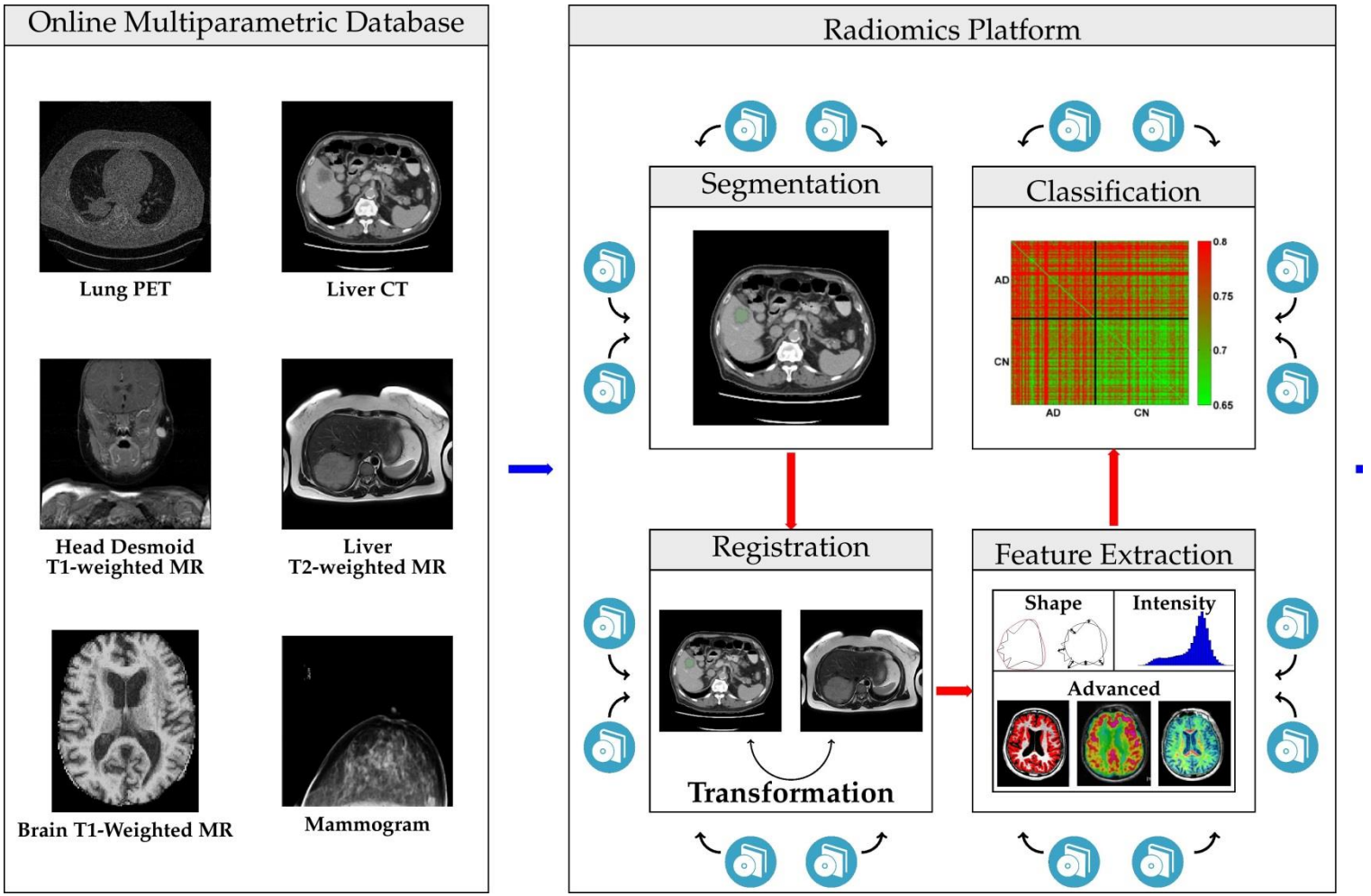
Can we predict DTF *CTNNB1* mutation status?

# Imaging – segmentation – feature extraction – prediction models



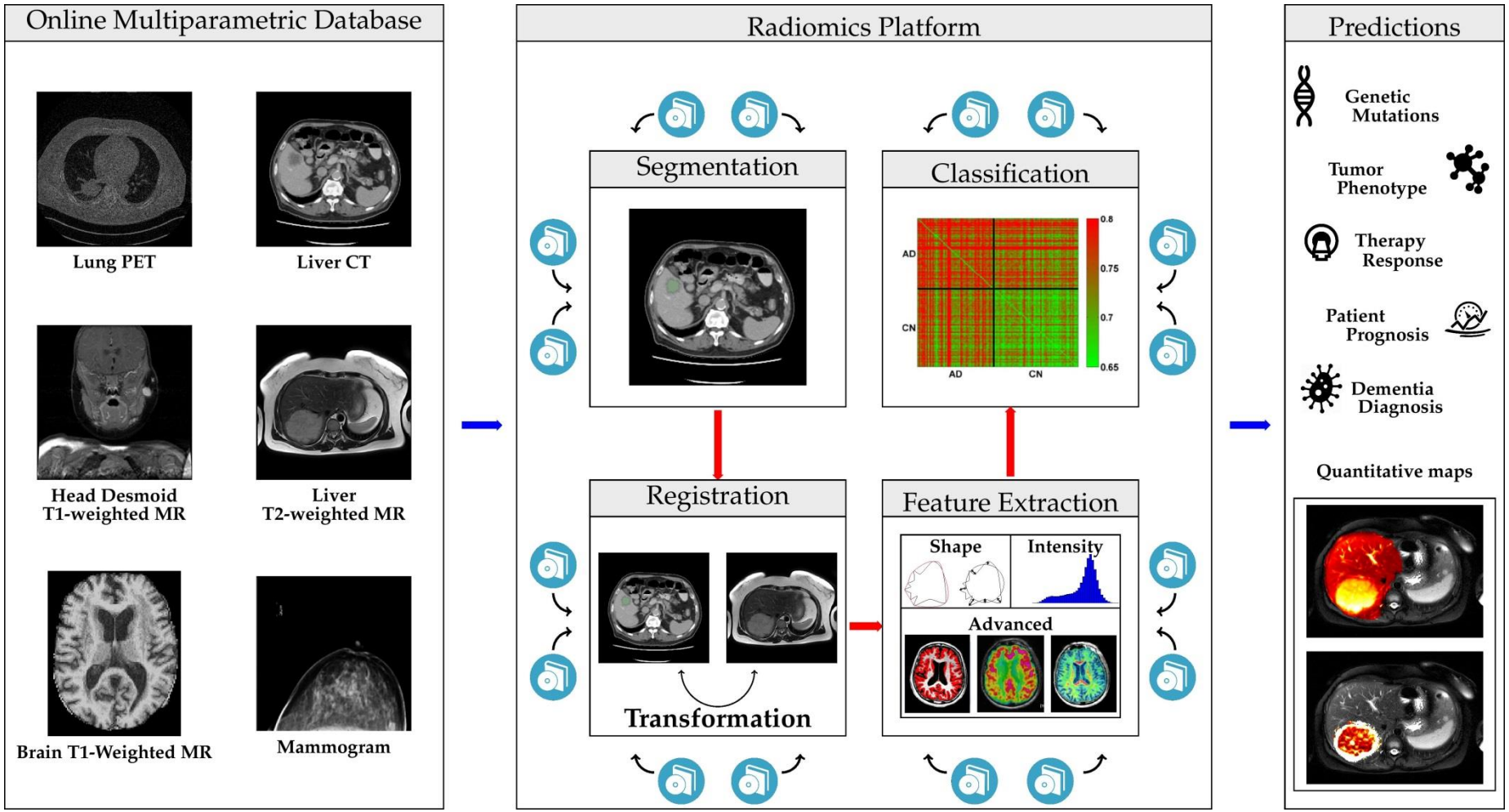

Erasmus MC Cancer Institute

# Imaging – segmentation – feature extraction – prediction models




Erasmus MC Cancer Institute

# Imaging – segmentation – feature extraction – prediction models

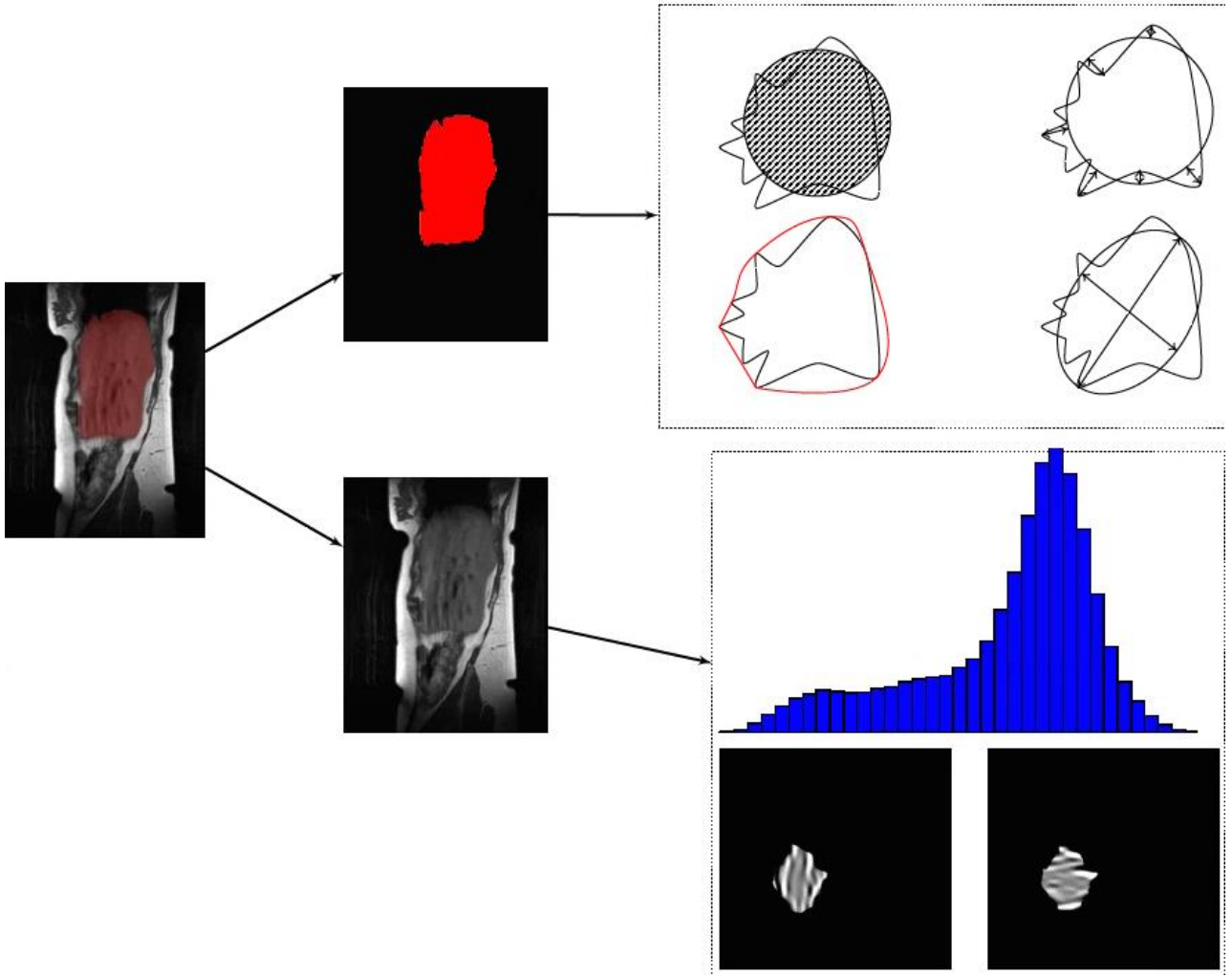



Erasmus MC Cancer Institute

# Using +/- 400 imaging features

**Semantic features**
e.g. age, gender, tumor location, pregnancy

**Computational features**
e.g. texture, shape, intensity and orientation

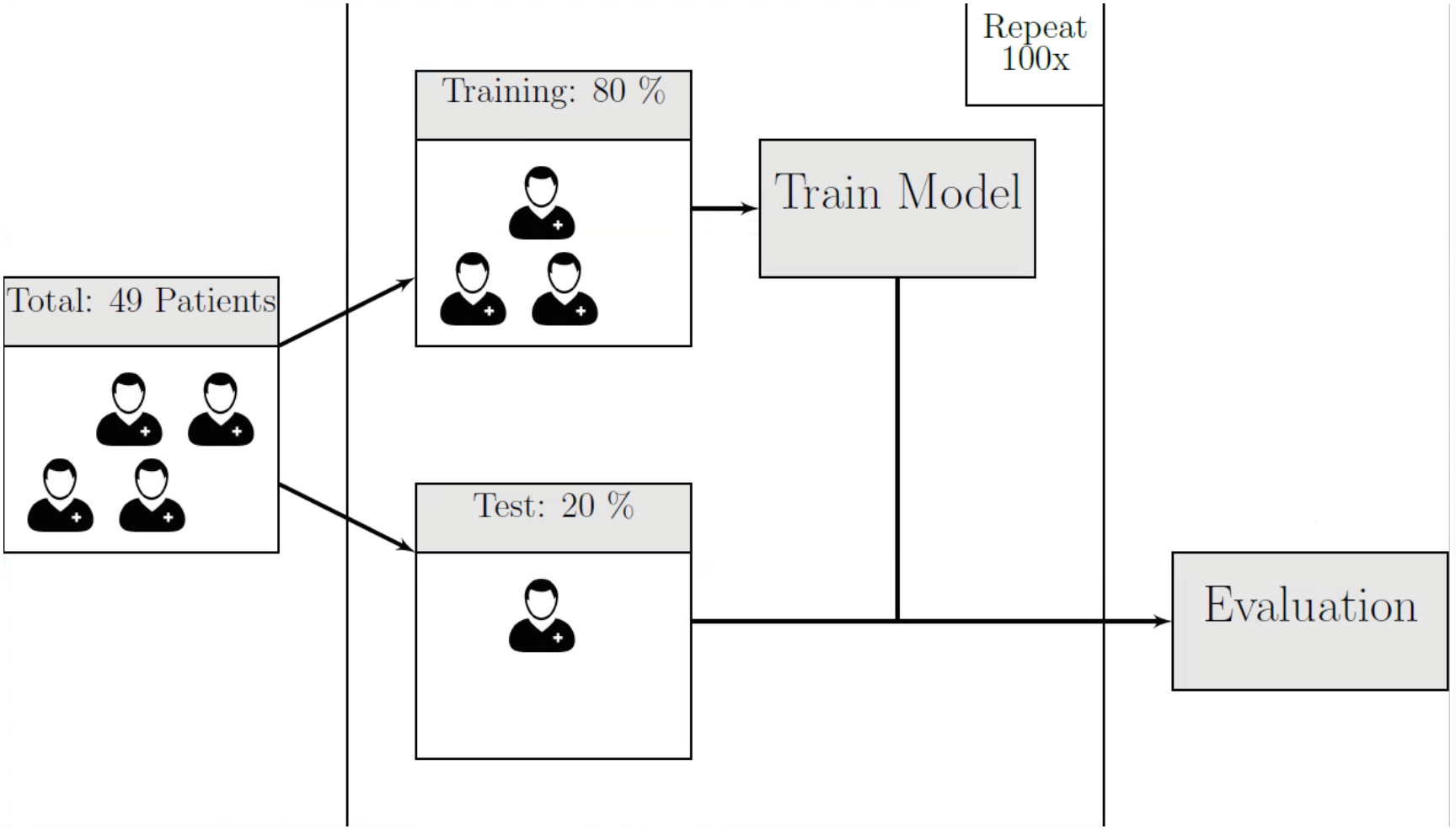


Erasmus MC Cancer Institute

## Can we predict DTF *CTNNB1* mutation status?

- Treatment naive extra-abdominal / abdominal wall DTF
- Known *CTNNB1* mutation or available formalin fixed parafin embedded samples
- T1 weighted MR imaging (spin-echo (SE) or gradient- echo (GRE))
- Between 2004 and 2017

# Cross-validation model




Erasmus MC Cancer Institute

# Can we predict DTF *CTNNB1* mutation status?

| | | Number of patients |
|---|---|---|
| **Gender** | male | 14 |
| | female | 35 |
| **Tumor location** | abdominal wall | 12 |
| | extra-abdominal | 37 |
| **CTNNB1 mutation** | T41A | 21 |
| | S45F | 11 |
| | Wild-type | 17 |

# The radiomics technique has a promising role for differentiating WT tumors from tumors with a *CTNNB1* mutation

| | T41A | S45F | WT |
|---|---|---|---|
| **Sensitivity [95% CI]** | **0.26** [0.06 – 0.41] | **0.11** [-.0.05 – 0.11] | **0.42** [0.20 – 0.64] |
| **Specitivity [95% CI]** | **0.78** [0.61 – 0.94] | **0.93** [0.83 – 1.02] | **0.87** [0.75 – 0.99] |
| **Area under the curve [95% CI]** | **0.58** [0.28 – 0.61] | **0.58** [0.43 – 0.73] | **0.75** [0.61 – 0.88] |

Erasmus MC Cancer Institute

## Which features are relevant?

T-test

No single significant features after correction for multiple testing

**Combination of features?**

## Conclusion from the pre-limary results

- Promising role for differentiating WT tumors

## Use of radiomics in clinical practice

- Prediction the *CTNNB1* mutation status does not change the diagnostic routine
- Biopsy is still needed to confirm the diagnosis

**Can we differentiate DTF tumors from other soft tissue tumors?**

## Can we differentiate DTF tumors from other soft tissue tumors?

- Treatment naive fibromyxosarcoma, myxoid liposarcoma and leiomyosarcoma of the **extremities**
- T1 weighted MR imaging
- 2004 and 2017

| Tumor type | Number of patients |
|---|---|
| Fibromyxosarcoma | 29 |
| Myxoid liposarcoma | 29 |
| Leiomyosarcoma | 29 |

## Challenges using radiomics in the clinical practice of DTF

Discovery phase study, no validation of findings

**Imaging**

Differences in imaging protocols, different scanning methods

T1W MR images, extrapolate to other sequences

**DTF**

Small sample size, create a bigger cohort

Poor DNA quality not able to obtain *CTNNB1* mutations

## Challenges using radiomics in the clinical practice of DTF

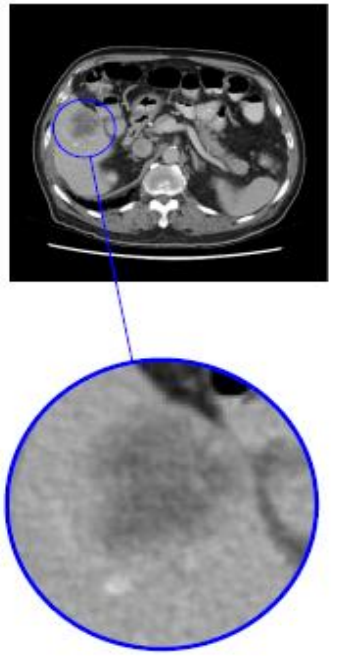
**Radiomics**

Learning curve in segmentation

Currently, semi-automatic segmentation → time consuming → automatic segmentation?

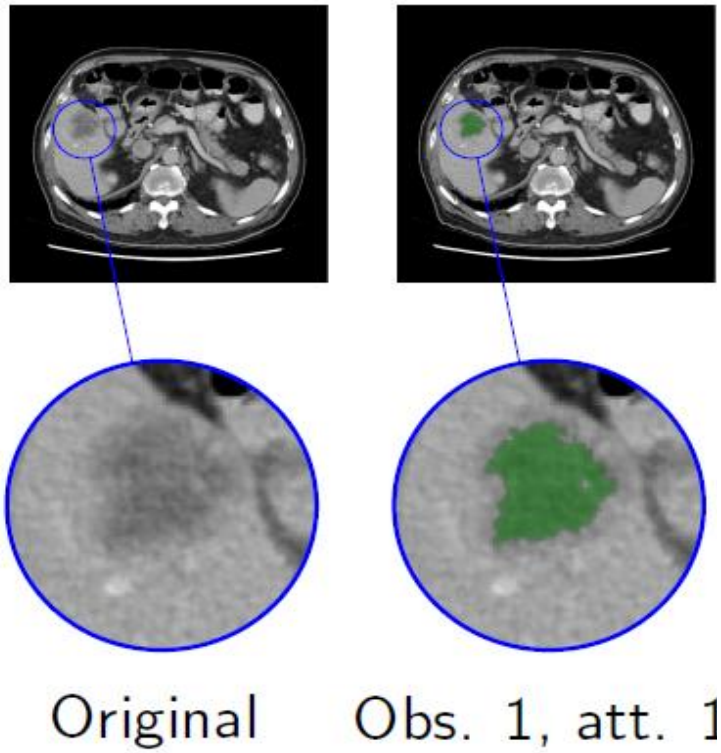
Inter- and intra observer differences

# Inter and intra-observer variability

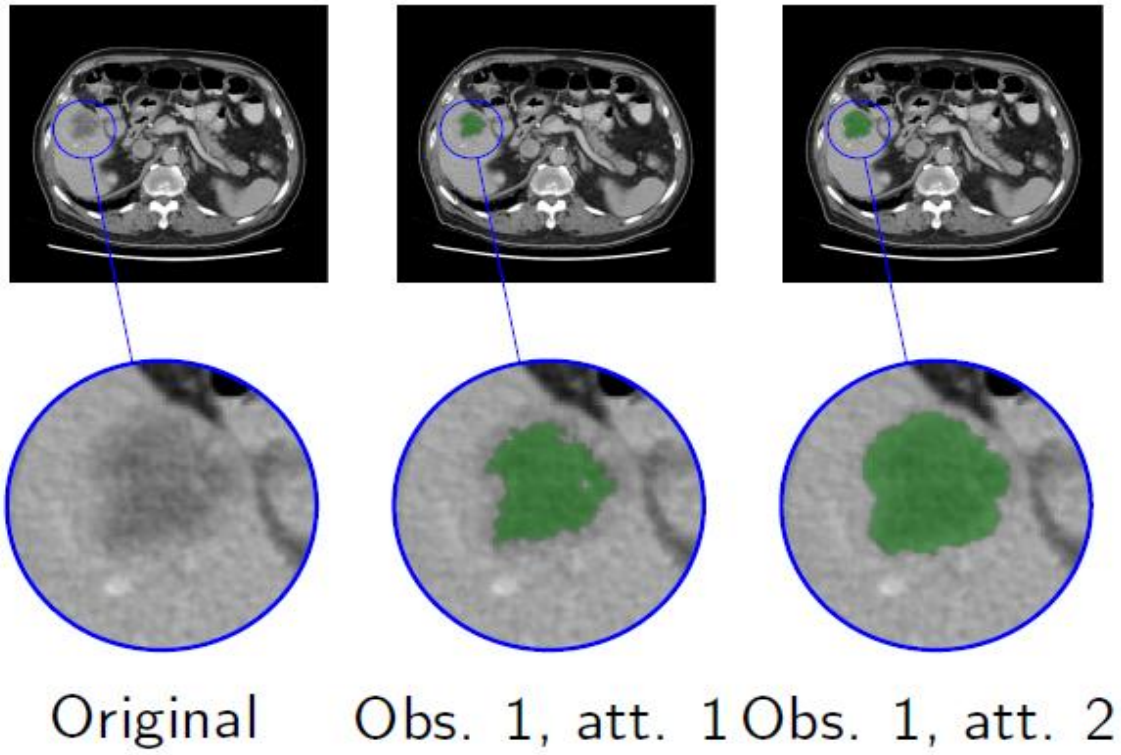


Original

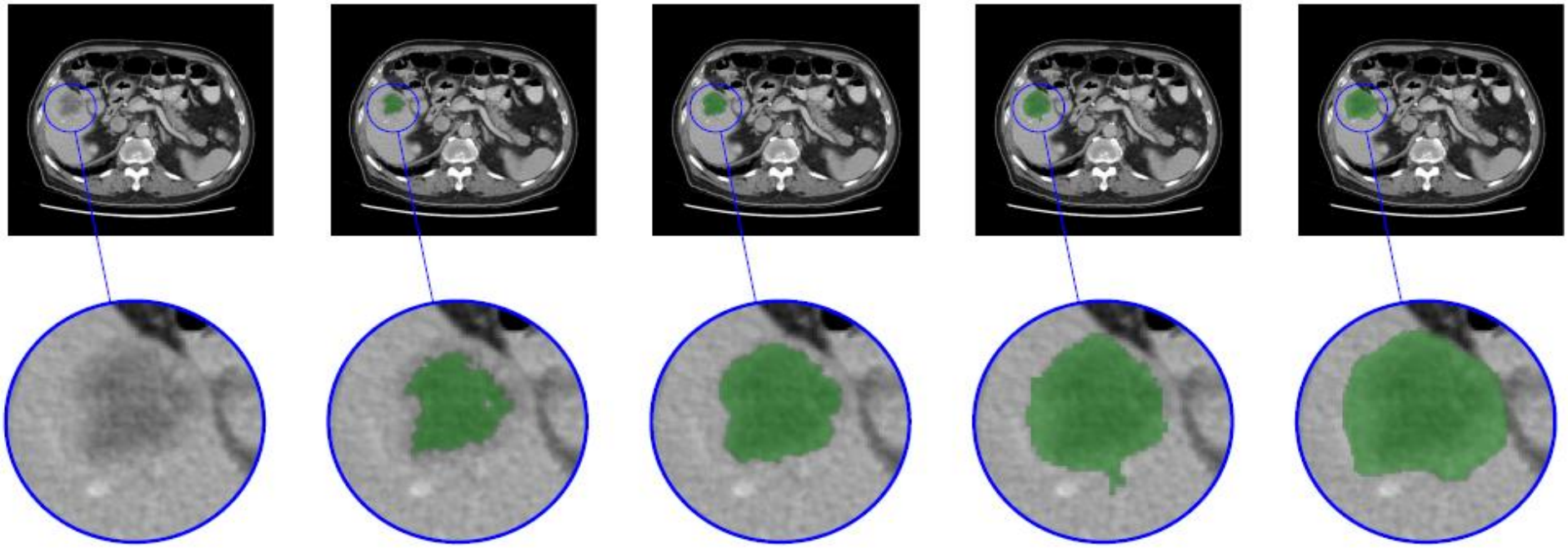
# Inter and intra-observer variability



# Inter and intra-observer variability



# Inter and intra-observer variability



## Radiomics is a promising new technique

### Future perspectives

Large cohort (multiple institutes)

Inclusion of multiple sequences

Imaging of DTF using a standard imaging protocol

Optimizing the radiomics platform and analysis (include more imaging features)

Using radiomics to quantify tumor progression / regression (e.g. tumor enhancement) over time

# References


1. Crago AM, Chmielecki J, Rosenberg M, et al.: Near universal detection of alterations in CTNNB1 and Wnt pathway regulators in desmoid-type fibromatosis by whole-exome sequencing and genomic analysis. Genes Chromosomes Cancer 2015;54:606-615.

2. Lazar AJ, Tuvin D, Hajibashi S, et al.: Specific mutations in the beta-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol 2008;173:1518-1527.

3. van Broekhoven DL, Verhoef C, Grünhagen DJ, et al.: Prognostic value of CTNNB1 gene mutation in primary sporadic aggressive fibromatosis. Ann Surg Oncol 2015;22:1464-1470.

4. Garvey PB, Booth JH, Baumann DP, et al.: Complex reconstruction of desmoid tumor resections does not increase desmoid tumor recurrence. Journal of the American College of Surgeons 2013;217:472-480.

5. Colombo C, Miceli R, Lazar AJ, et al.: CTNNB1 45F mutation is a molecular prognosticator of increased postoperative primary desmoid tumor recurrence: an independent, multicenter validation study. Cancer 2013;119:3696-3702.

6. Gevaert O, Echegaray S, Khuong A, Hoang CD, Shrager JB, Jensen KC, et al. Predictive radiogenomics modeling of EGFR mutation status in lung cancer. Sci Rep. 2017;7:41674.

7. Karlo CA, Di Paolo PL, Chaim J, Hakimi AA, Ostrovnaya I, Russo P, et al. Radiogenomics of clear cell renal cell carcinoma: associations between CT imaging features and mutations. Radiology. 2014;270:464-71.

https://github.com/MStarmans91/WORC


**Milea Timbergen**
m.timbergen@erasmusmc.nl

**Martijn Starmans**
m.starmans@erasmusmc.nl

Department of Medical Oncology
Stefan Sleijfer
Melissa Vos

Department of Surgical Oncology
Kees Verhoef
Dirk Grünhagen

Department of Medical Informatics
Wiro Niessen
Stefan Klein

Department of Radiology
Jacob Visser
Guillaume Padmos

Department of pathology
Geert van Leenders

STICHTING COOLSINGEL

Erasmus MC Cancer Institute