BBS Seminar: AI in Clinical Research and Drug Development and BBS General Assembly

Automated Total Metabolic Tumor Volume (aTMTV) and its Performance Assessment

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on behalf of the aTMTV model validation study team

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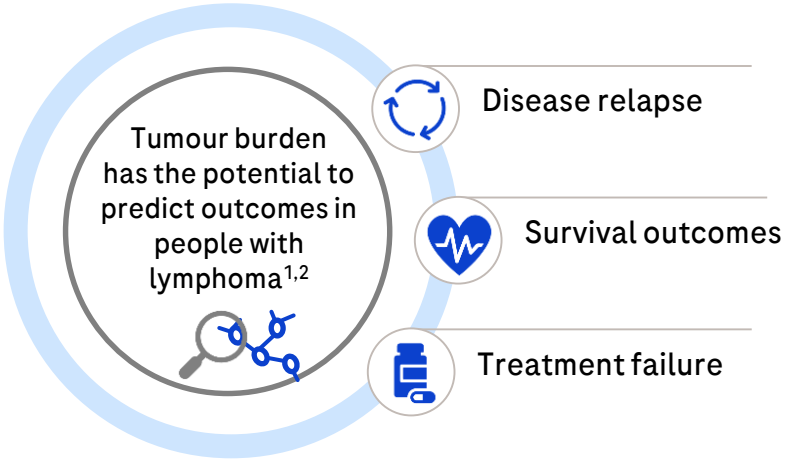
Total metabolic tumour volume (TMTV) is a measure of total tumour burden [1]

TMTV is a quantitative radiological measurement of the total volume of all lesions visualised on FDG-PET/CT scans and has potential prognostic value in some lymphoma types



Example studies showing prognostic value of pre-treatment TMTV in different settings

	DLBCL[3]		Follicular lymphoma[4]		Hodgkin lymphoma[5]	
Pretreatment TMTV, cm^3	≤ 300	> 300	≤ 510	> 510	≤ 147	> 147
5-year PFS rate, %	75	42	65	33	92	71

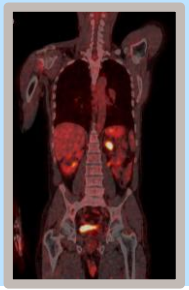
CT, computed tomography; FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography; SUV, standardised uptake value; TMTV, total metabolic tumour volume. 1. Barrington SF, Meignan M. *J Nucl Med* 2019;60:1096–102; 2. El-Galaly TC *et al. Br J Haematol* 2022;197:139–55; 3. Capobianco N *et al. J Nucl Med* 2021;62:30–6; 4. Jemaa S *et al. Cancer Imaging* 2022;22:39;

Manual evaluation limit the broad adoption of Total metabolic tumour volume (TMTV)

The assessment of TMTV requires the segmentation of all malignant foci in the body

A threshold may be applied to distinguish between physiological and pathological FDG-uptake – this may be calculated as either 41% of the maximum SUV, or a fixed SUV threshold of 2.5 or 4.0 may be applied[1,2]

Semi-automated visualisation software can be used to define volumes of interest around the tumour, which are then manually adjusted by the radiologist or nuclear medicine physician based on their prior knowledge and experience[3,4]



Current methods for delineating all tumour regions are challenging and time-consuming [1,3,5,6]

The optimal cut-off value for determining the prognostic significance of TMTV has not yet been defined [2]

SUV thresholding methods for tumour segmentation have not been standardised or validated for use in clinical research and practice [1,2]

CT, computed tomography; FDG, 18F-fluorodeoxyglucose; PET, positron emission tomography; SUV, standardised uptake value; TMTV, total metabolic tumour volume. 1. Barrington SF, Meignan M. *J Nucl Med* 2019;60:1096–102; 2. El-Galaly TC *et al. Br J Haematol* 2022;197:139–55; 3. Capobianco N *et al. J Nucl Med* 2021;62:30–6; 4. Jemaa S *et al. Cancer Imaging* 2022;22:39; 5. Meignan M *et al. Br J Radiol* 2021;94:20210448; 6. Weisman AJ *et al. Radiol Artif Intell* 2020;2:e200016

aTMTV is a machine-learning-based tumour assessment tool in development for use in people with FDG-avid lymphoma

Algorithm developed at Genentech

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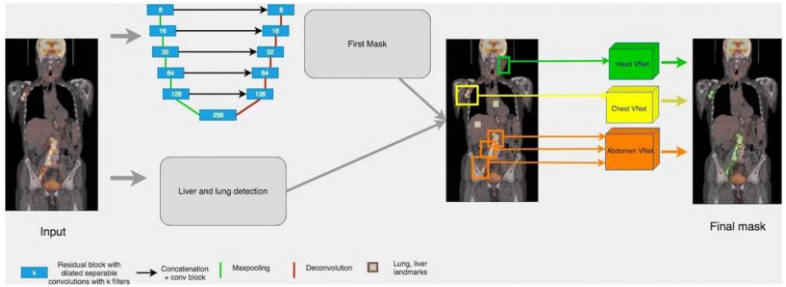
Rick Carano (Genentech)

Jemaa S *et al. J Digit Imaging* 2020



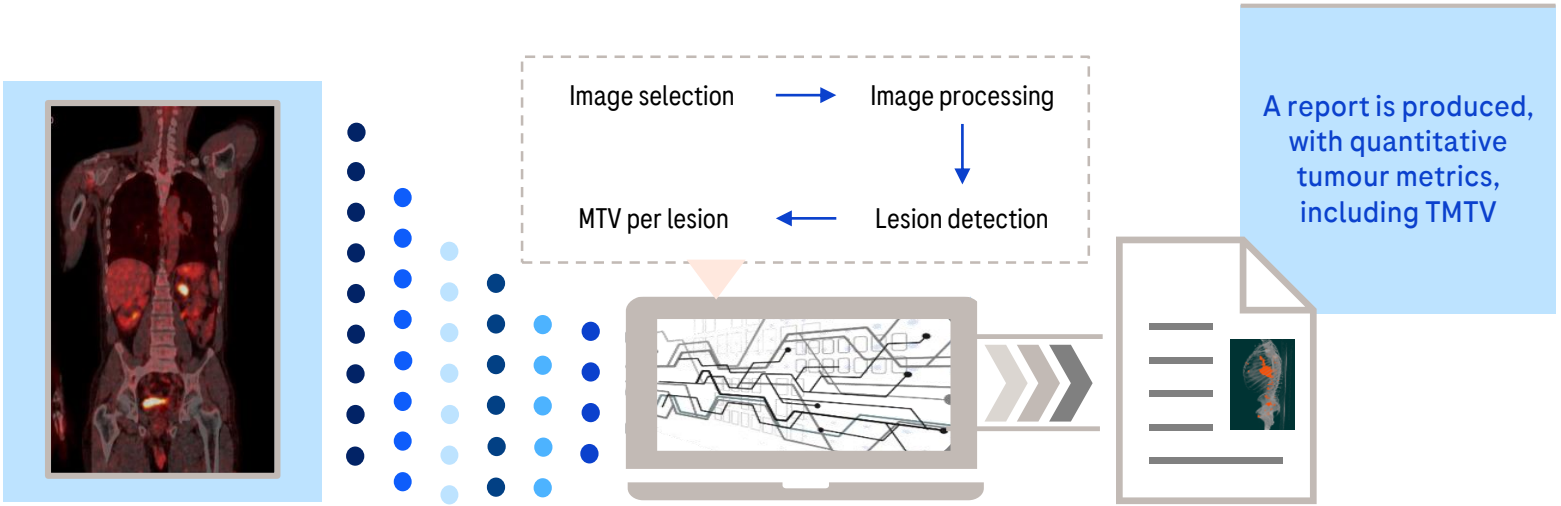
aTMTV is a machine-learning-based algorithm currently in development, which aims to automate lesion segmentation, lesion visualisation and TMTV assessment from whole-body FDG-PET/CT scans of people with FDG-avid lymphoma

- Quantitative assessment of all FDG-avid lesions
- Faster, automated alternative to a labour-intensive radiology assessment
- Enabling the standardisation of methods for TMTV measurement to support its use in clinical practice

aTMTV is an investigational device currently in development. aTMTV, automated total metabolic tumour volume; CT, computed tomography; FDG, 18F-fluorodeoxyglucose; mTMTV, manual total metabolic tumour volume; PET, positron emission tomography; TMTV, total metabolic tumour volume

1. Jemaa S *et al. J Digit Imaging* 2020;33:888–94; 2. Jemaa S *et al. Cancer Imaging* 2022;22:39.

aTMTV automates FDG-PET/CT scan analyses



FDG-PET/CT scan	Curation and pre-processing	Lesion detection and segmentation	Feature extraction	Final output metrics

aTMTV is an investigational device currently in development. aTMTV annotated images can be reviewed or edited by appropriately trained physicians. aTMTV, automated total metabolic tumour volume; CT, computed tomography; FDG, 18F-fluorodeoxyglucose; MTV, metabolic tumour volume; PET, positron emission tomography; TMTV, total metabolic tumour volume.

aTMTV was trained and tested using a large, multicentre clinical trial dataset

aTMTV was trained and tested using retrospective data extracted from two large, phase 3 multicentre trials in DLBCL and FL[1,2]

Training set
Baseline and post-treatment FDG-PET/CT scans from 836 participants with DLBCL from 235 different study sites[3,4] (the GOYA study)

Independent test set
Baseline and post-treatment FDG-PET/CT scans from 166 participants with DLBCL (the GOYA study) and 201 participants with FL (the GALLIUM study)[3,4]

Methods for assessing model performance[3,4]

- Pearson's correlation coefficient (*r*) was used to evaluate the performance of aTMTV versus an expert radiologist
- Bias and variances were assessed using a weighted Deming regression and Bland–Altman analysis, respectively
- Lesion detection performance was evaluated based on sensitivity and positive predictive values

GOYA, NCT01287741; GALLIUM, NCT01332968. FDG-PET/CT scans were acquired according to a standardised imaging charter using a range of scanner models. aTMTV, automated total metabolic tumour volume; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FDG, 18F-fluorodeoxyglucose; FL, follicular lymphoma; PET, positron emission tomography. 1. Jemaa S *et al. Blood* 2019;134(Suppl 1):4666; 2. Jemaa S *et al. J Digit Imaging* 2020;33:888–94; 3. Xu. T. *et al.* Poster presented at 2023 European Hematology Association (EHA) Hybrid Congress, June 8–15, 2023. 4. Xu T. *et al.* Poster presented at the 17th International Conference on Malignant Lymphoma (ICML), June 13–17, 2023.

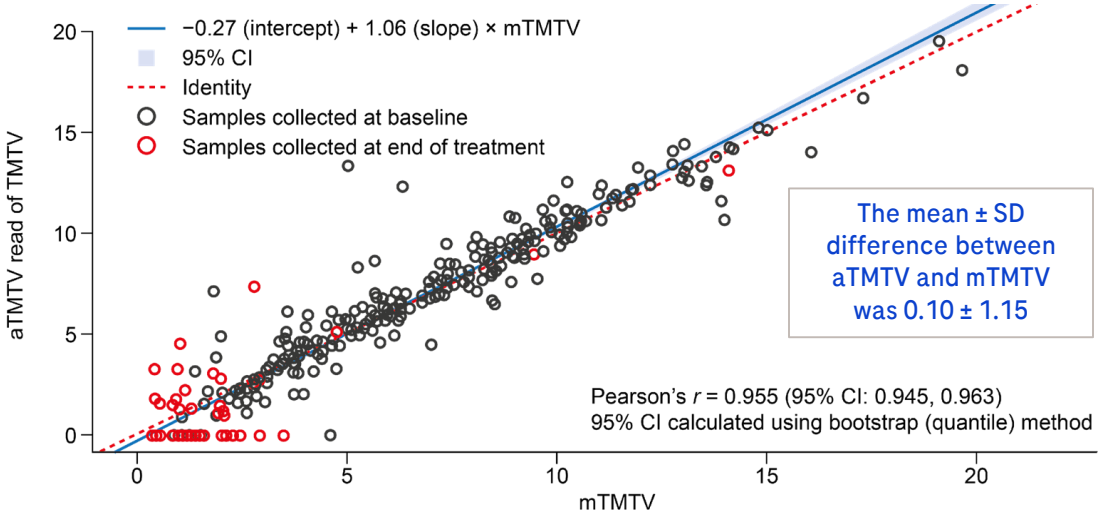
Samples selected for aTMTV performance exploratory study

Characteristic, n (%)	Overall n = 367	Patients with DLBCL (from GOYA) n = 166	Patients with FL (from GALLIUM) n = 201
Sex, female	208 (56.7)	85 (51.2)	123 (61.2)
Age, group, years			
< 65	237 (64.6%)	98 (59.0)	139 (69.2)
≥ 65	130 (35.4%)	68 (41.0)	62 (30.8)
Ethnicity			
Hispanic or Latin	33 (9.0%)	14 (8.4)	19 (9.5)
Not Hispanic or Latin	304 (82.8%)	146 (88.0)	158 (78.6)
Not reported or unknown	30 (8.2%)	6 (3.6)	24 (11.9)
ECOG Performance Status			
0 or 1	343 (93.5%)	148 (89.2)	195 (97.0)
2 or 3	24 (6.5%)	18 (10.8	6 (3.0)
Presence of bulky disease	153 (41.7%)	60 (36.1)	93 (46.3)
> 1 extra-nodal site	233 (63.5%)	113 (68.1)	120 (59.7)
Bone marrow involvement, Yes	125 (34.1%)	17 (10.2)	108 (53.7)

aTMTV correlation with mTMTV[1,2]

Model testing

Deming regression fit between aTMTV versus mTMTV in cubic root
(N = 367 participants with DLBCL or FL)



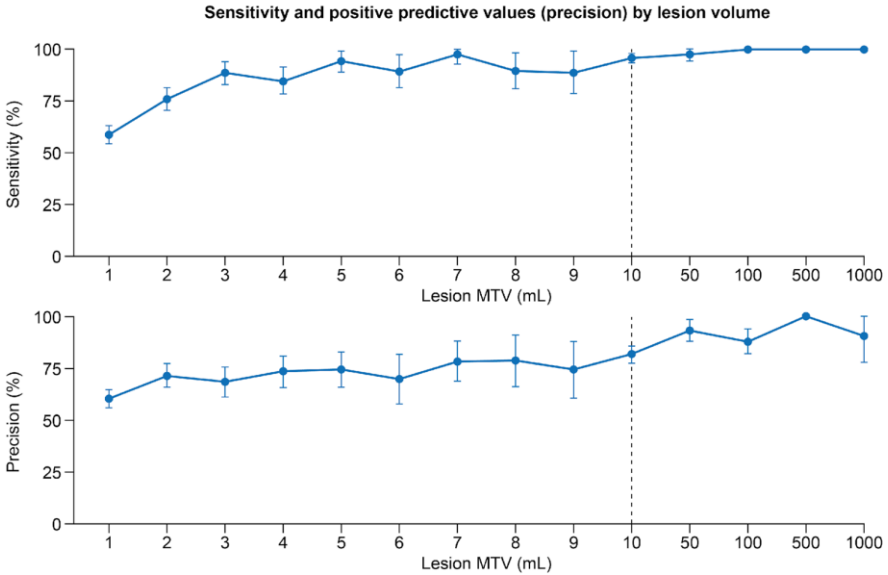
A slope of 1.06 (95% CI: 1.02, 1.09) and intercept of −0.27 (95% CI: −0.52, −0.03) indicate a lack of systematic bias between aTMTV quantification and mTMTV in people with DLBCL or FL

Agreement between aTMTV and mTMTV was consistent among patients with different demographics, clinical characteristics, and across scans from different PET/CT scanner manufacturers

aTMTV, automated total metabolic tumour volume; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; mTMTV, manual read of total metabolic tumour volume; TMTV, total metabolic tumour volume. 1. Xu. T. *et al.* Poster presented at 2023 European Hematology Association (EHA) Hybrid Congress, June 8–15, 2023. 2. Xu T. *et al.* Poster presented at the 17th International Conference on Malignant Lymphoma (ICML), June 13–17, 2023.

aTMTV lesion detection performance[1,2]

Model testing



Detection performance was lower for lesions ≤ 10 mL (sensitivity, 67%; precision, 72%) than for lesions > 10 mL (sensitivity and precision > 95%)

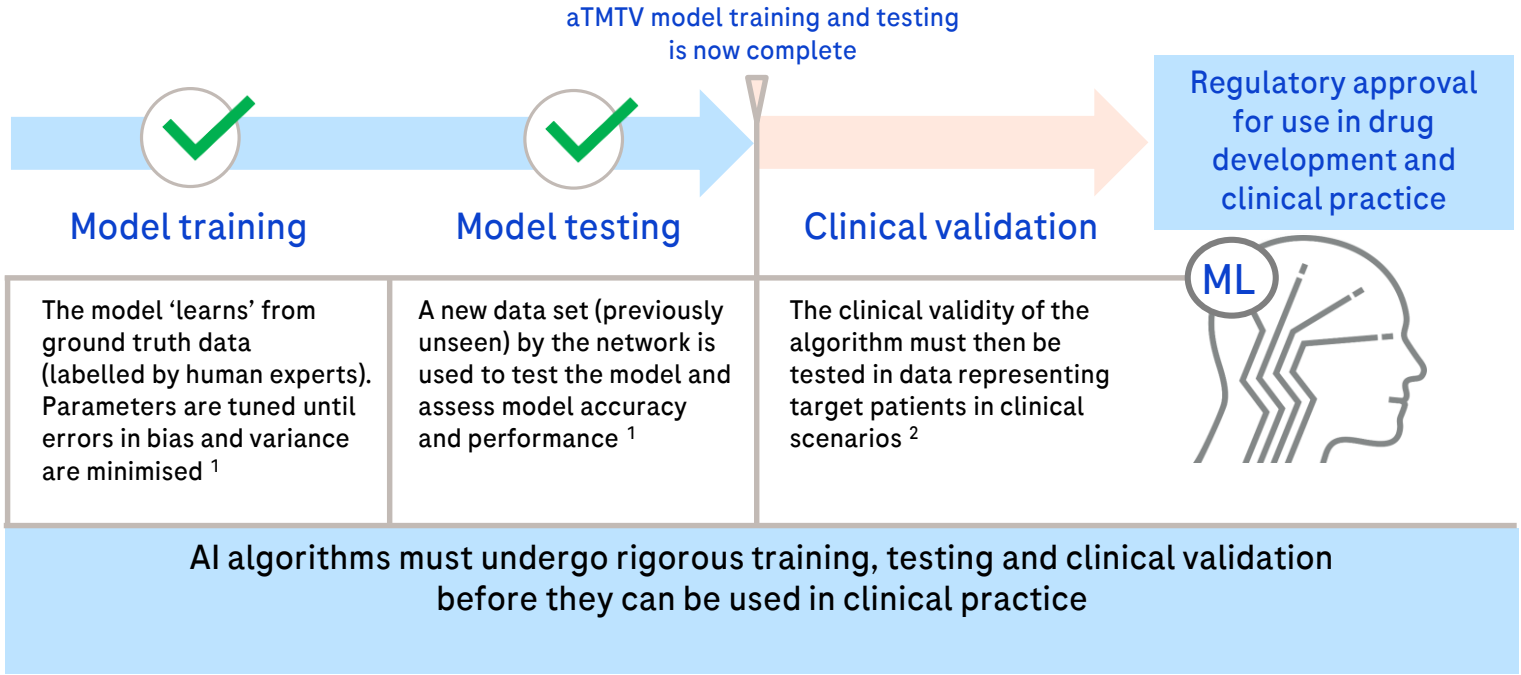
Reduced algorithm performance for lesions ≤ 10 mL may be the result of higher variability among readers in the determination of small lesions; future work aims to optimise performance for use in clinical practice

lesions also detected by aTMTV

detected manually

The combined test set included 367 participants with DLBCL and FL. Sensitivity and positive predictive values (precision) are first calculated per patient, then summarised as mean values for the patient population. aTMTV, automated total metabolic tumour volume; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; mTMTV, manual read of total metabolic tumour volume; MTV, metabolic tumour volume; TMTV, total metabolic tumour volume. 1. Xu. T. *et al.* Poster presented at 2023 European Hematology Association (EHA) Hybrid Congress, June 8–15, 2023. 2. Xu T. *et al.* Poster presented at the 17th International Conference on Malignant Lymphoma (ICML), June 13–17, 2023.

Clinical validation is the next stage of aTMTV development and a step closer towards regulatory approval



aTMTV, automated total metabolic tumour volume; ML machine learning. 1. Borstelmann SM. *Acad Radiol* 2020;27:13–25; 2. Park SH *et al. Korean J Radiol* 2021;22:442–53

Doing now what patients need next