Whole genome sequencing (WGS) can classify diagnostically challenging tumors (1133P)

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Background

- Cancer of unknown primary (CUP) remains an ongoing clinical challenge
- Genomic characterization can be used for tumor type prediction[1,2,3]
- A WGS-based tumor type '**cancer of unknown primary prediction algorithm**' (CUPPA) was developed, validated, and applied to 47 patients with a diagnostically challenging tumor

Methods

- CUPPA combines three DNA classifiers into an overall prediction (fig. 1)[2, 4, 5]
- Predictive performance of CUPPA was analyzed in a validation cohort of samples with known tumor origin (n=451)
- CUPPA was applied to **23 patients with a CUP** and 24 patients with an inconclusive diagnosis

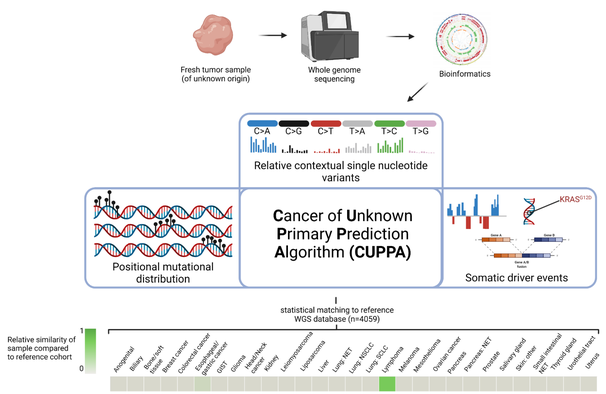

Figure 1. Schematic overview of CUPPA workflow

WGS is performed on a fresh tumor sample (of unknown primary). After standardized bioinformatics, the CUPPA algorithm can be applied. Within the CUPPA algorithm, three orthogonal DNA classifiers, each with predictive power for tissue of origin, were combined into an overall prediction. Samples (of unknown origin) are assigned a relative similarity likelihood to each primary cancer origin cohort.

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Predictive performance of CUPPA (validation cohort)

- Correct classification in 380/451 samples of known origin (tab. 1)
- High predictive accuracy across majority of tumor types (fig. 2)
- Similarity likelihood score can be used to increase prediction confidence (fig. 3)

Overall test performance and performance per tumor type

Accuracy	84%
Precision (positive predictive value	86%
Sensitivity (recall)	84%
F1	85%

Table 1. Micro-averaged predictive performance parameters over the total validation cohort

F1 = harmonic mean of precision and recall

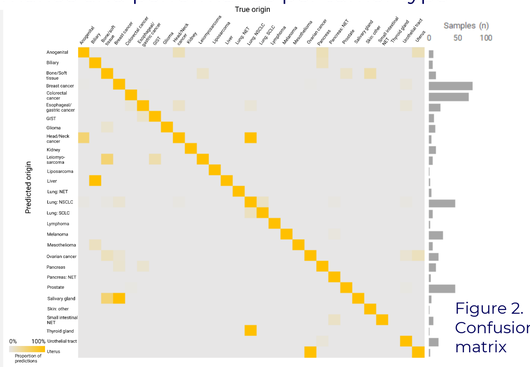


Figure 2. Confusion matrix

At a 0.8 cut-off in the similarity likelihood score, a 95% predictive accuracy was achieved. 341/451 (75%) of samples had a score of ≥0.8

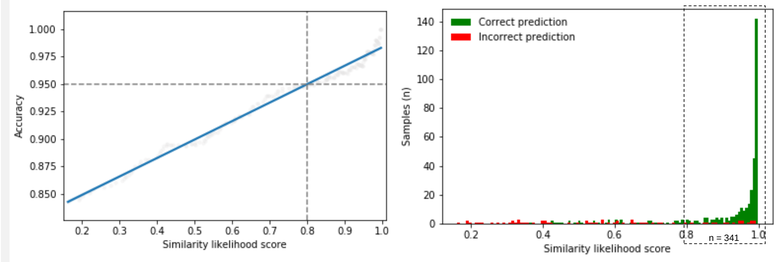
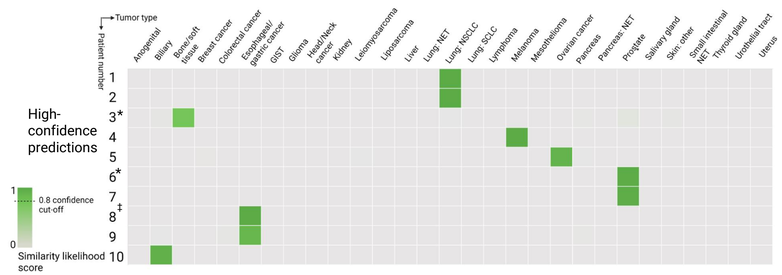


Figure 3. Accuracy scores at different test cut-off values (A) and histogram showing distribution of similarity likelihood scores (B)

Clinical utility of CUPPA

A high-confidence prediction was reached for 10/23 CUP patients



In 4/13 low-confidence predictions, expert pathologist(s) indicated the prediction to be informative within the clinicopathological context to narrow differential diagnosis

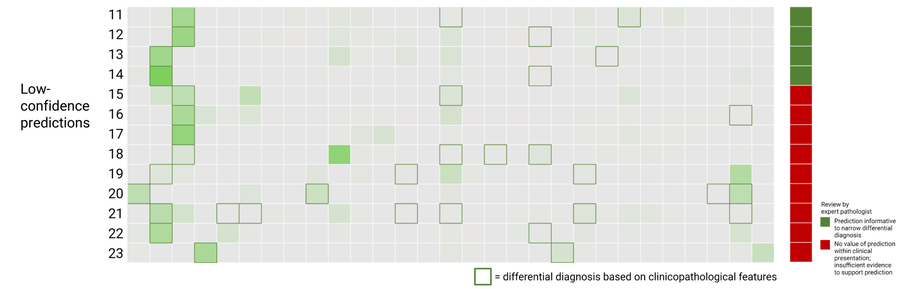


Figure 4. Per patient overview of CUPPA predictions in CUP patients

*Diagnosis was further supported by presence of an EWSR1-WT1 fusion in patient 3 and a TMPPRS2 - ERG fusion in patient 6.
‡ Patient 8 underwent a second gastroscopy after WGS analysis. In contrast to previous endoscopic examination, a malignant lesion was detected and biopsied, confirming the diagnosis.

In 24 patients with an inconclusive final diagnosis, a high-confidence prediction alleviated diagnostic uncertainty in 17 patients (data not shown). In total, **WGS/CUPPA provided diagnostic insights in 31/47 patients** with a diagnostically challenging tumor (fig. 5)

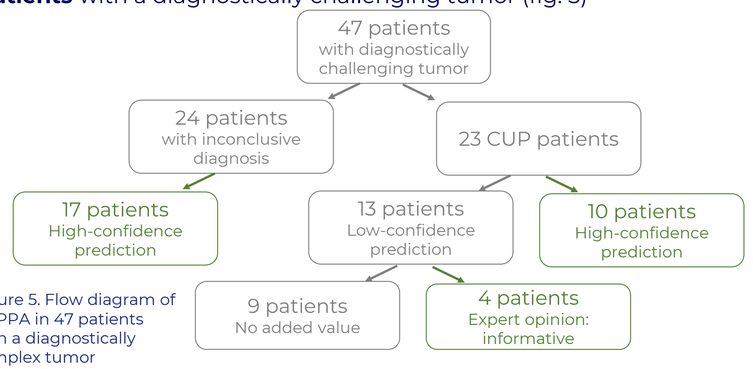


Figure 5. Flow diagram of CUPPA in 47 patients with a diagnostically complex tumor

Conclusions

- CUPPA can classify 75% of tumors of known origin with **95% predictive accuracy** based on a high-confidence prediction
- When applied to CUP patients, a high-confidence prediction provided a **probable diagnosis in 10/23 patients**. Low-confidence predictions could be used to **guide differential diagnoses** in 4/13 CUP patients
- Diagnostic uncertainty could be alleviated in 17/24 inconclusive cases
- CUPPA algorithm can **assist clinical decision making** in diagnostically complex tumors

1. Nat Commun. 2021 May 24;12(1):3051; 2. Nat. Commun. 2020 Feb 5;11(1):728; 3. JAMA Oncol. 2020 Jan 1;6(1):84-91; 4. Nature. 2020 Feb;578(7793):94-101; 5. Nat. Rev. Cancer 2006 Aug;6(8):593-602)