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Molecular classification of cancers of unknown primary expands and refines treatment options

D. George[1], E. Moore[2,*], G. Blobe[3], N. Devito[4], B. Hanks[5], M. Harrison[6], C. Hoimes[3], J. Jia[7], M. Morse[7], P. Jayaprakasan[8], A. Mackelfresh[1], H. Mulder[8], K. Beauchamp[2], J. Michuda[2], M. Stumpe[2], E. Perakslis[8], T. Taxter[2]

[1]Duke University Medical Center, Durham, US // [2]Tempus Labs, Inc., Chicago, US // [3]Duke Cancer Institute, Durham, US // [4]Duke University, Durham, US // [5]Duke Cancer Center - Duke University Medical Center, Durham, US // [6]Snyderman Genome Science Research Building, Durham, US // [7]Duke Cancer Center, Durham, US // [8]Duke Clinical Research Institute, Durham, US

INTRODUCTION

Patients with cancer of unknown primary (CUP) present a clinical challenge due to complicated diagnostic workups and empirically-selected platinum-based regimens that may not be the most active first line for the primary disease. The Tempus Tumor Origin (TO) test is a CAP/CLIA validated molecular diagnostic classifier that uses RNA-Seq data to identify the most likely cancer type or subtype from 68 possible diagnoses. Despite the importance of cancer type identification in advising guideline-based treatment, prior studies of molecular classifiers have found unclear clinical impact.

METHODS

We retrospectively analyzed de-identified records from 289 patients in the Tempus clinico-genomic database who received a CUP diagnosis; all had NGS and Tempus TO testing ordered by the treating clinician. Two oncologists separately reviewed available clinical information for each patient—including imaging, pathology, and NGS reports— to determine the course of treatment before they reviewed results from the diagnostic classifier and evaluated whether the predicted diagnosis would change treatment. Disagreement was adjudicated by a third reviewer.

	CUP Patients (N=289)
Age (yrs)	
Mean (SD)	66.1 (11.3)
Median (Q1, Q3)	66.0 (59.0, 73.0)
Female	145 (50.2%)
Biopsy Site	
Liver	87 (30.1%)
Abdomen	54 (18.7%)
Bone and soft tissue	28 (9.7%)
Lung	22 (7.6%)
Head and neck	22 (7.6%)
Thorax	21 (7.3%)
GI tract	12 (4.2%)
Other	43 (14.9%)
Prediction Probability of TO Primary Diagnosis	
Mean (SD)	77.1% (20.6%)
Median (Q1, Q3)	84.0% (61.0%, 95.0%)

Table 1. Overview of demographic and clinical data.

SUMMARY

- Following review of Tempus TO test results, expert recommendations for therapeutic management were altered in 81% of patients with confirmed cancers of unknown primary.
- Therapy changes include the addition and removal of chemotherapy and checkpoint inhibitors (CPI), as well as alterations in radiation and surgical treatments, highlighting the potential of molecular classifiers to provide clinical insight into the management of CUP patients.

RESULTS

Review of TO classifier results leads to altered treatment recommendations and increased confidence

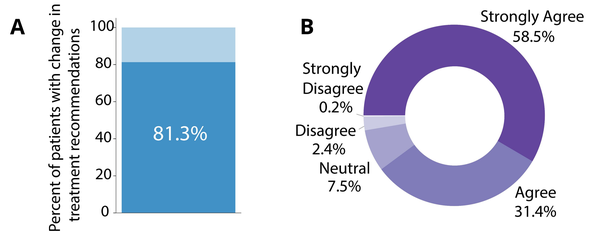

Figure 1. A) Consensus treatment recommendations were changed for 235 out of 289 patients following review of classifier results. B) From 414 reviews, clinicians rated their agreement with the statement: "The TO result increased my confidence in selecting the most appropriate treatment regimen".

Integrating molecular diagnostic classification results with DNA variant-level analysis

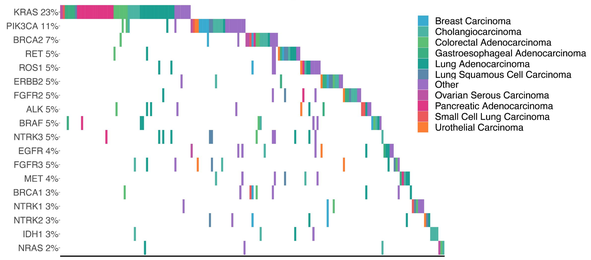

Figure 2. NGS sequencing panel results highlight the association between clinically-relevant mutations and predicted subtypes, emphasizing scenarios where an accurate diagnosis is important for clinical management decisions.

Breakdown of individual reviews according to survey responses

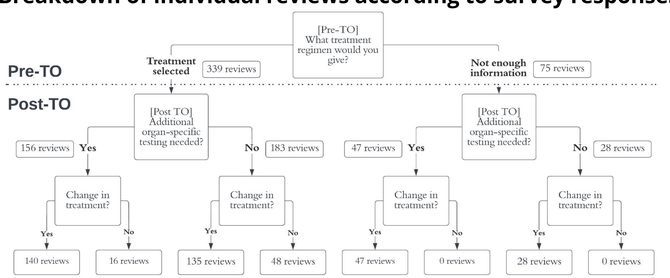

Figure 3. From 289 patients, we analyzed 414 reviews: 2 reviews each for the 125 patients with agreement on primary endpoints and 1 consensus, adjudicated review for the 164 patients with initial disagreement as to whether the patient was CUP or whether classifier results would alter treatment.

Primary predicted diagnosis	n
Cholangiocarcinoma	58 (20.1%)
Lung adenocarcinoma	41 (14.2%)
Pancreatic adenocarcinoma	22 (7.6%)
Lung squamous cell carcinoma	19 (6.6%)
Colorectal adenocarcinoma	18 (6.2%)
Gastroesophageal adenocarcinoma	18 (6.2%)
Urothelial carcinoma	13 (4.5%)
Breast carcinoma	12 (4.2%)
Ovarian serous carcinoma	11 (3.8%)
Small cell lung carcinoma	9 (3.1%)
Head and neck squamous cell carcinoma	7 (2.4%)
Other (31 subtypes)	61 (21.1%)

Table 2. Top predicted subtypes from the molecular diagnostic classifier from 289 patients.

Alterations to therapeutic management

Removed therapies	n (135 reviews)
Fluorouracil	46 (34.1%)
Oxaliplatin	42 (31.1%)
Carboplatin	41 (30.4%)
Paclitaxel	37 (27.4%)

Table 3. 135 reviews specified a treatment prior to review of classifier results that was altered after review (with no additional testing recommended).

Added therapies	n (163 reviews)
Gemcitabine	69 (42.3%)
Cisplatin	62 (38.0%)
CPI	26 (16.0%)
Tyrosine kinase inhibitor	13 (8.0%)

Table 4. Most common and clinically relevant added therapies from the 163 reviews with a change in treatment following review of classifier results (with no additional testing recommended).

	n
Therapy changes	**135 reviews**
Updated chemo	87 (64.4%)
Removed chemo, CPI only	8 (5.9%)
Systemic to local	4 (3.0%)
Additional testing	**203 reviews**
PD-L1	118 (58.1%)
Additional imaging	60 (29.6%)
ER/PR/HER2	31 (15.3%)
HRD	19 (9.4%)

Table 5. Categorical therapy changes and additional tests ordered based on applicable reviews.

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