Self-assessment of adherence to the Ten Simple Rules of Credible Practice in Modeling and Simulation in Healthcare

Tumor microenvironment governs the prognostic landscape of immunotherapy for head and neck squamous cell carcinoma: A computational model-guided analysis.

The current self-assessment is in accordance with Erdemir et al. (2020). The rubric can be accessed at: https://www.imagwiki.nibib.nih.gov/content/10-simple-rules-conformance-rubric

Date of self-assessment: August 29, 2024

Model files and documentation:

Rule 1: Define context clearly: Develop and document the subject, purpose, and intended use(s) of the model or simulation.

Current Conformance Level: Comprehensive

Model Context: Cell-state-specific mechanistic model of the tumor microenvironment (TME) for head and neck squamous cell carcinoma (HNSCC) in the presence (absence) of Immune checkpoint inhibitor treatment (ICI).

Primary goal of the model/tool/database: The primary goal of the modeling exercise was to leverage the TME-wide mechanistic models to explain (a) the existence of distinct compositional possibilities of the HNSCC TME and (b) how these compositional possibilities play a governing role in determining the response to ICI therapy. Additionally, the proposed model predicts the potential targets and biomarkers towards an improved ICI response.

Biological Domain of the Model: Cellular state
Structures of the Model: Tumor microenvironment
Spatial Scales Included in the Model: N/A (Assumes spatial homogeneity)
Time Scales Included in the Model: Week-Month

Rule 2: Use contextually appropriate data: Employ relevant and traceable information in the development or operation of a model or simulation.

Current Conformance Level: Adequate

Data for building the model	**Published?**	**Private?**	**How is credibility checked?**	**Current Conformance Level**
in vitro (primary cells cell, lines, etc.)	N/A	N/A	N/A	N/A
ex vivo (excised tissues)	N/A	N/A	N/A	N/A
in vivo pre-clinical (lower-level organism or small animal)	N/A	N/A	N/A	N/A
in vivo pre-clinical (large animal)	N/A	N/A	N/A	N/A
Human subjects/clinical	Yes	No	The source data used for model construction is qualitative and the related clinical protocols have been published in peer-reviewed journals	Adequate

Data for validating the model	**Published?**	**Private?**	**How is credibility checked?**	**Current Conformance Level**
in vitro (primary cells cell, lines, etc.)	N/A	N/A	N/A	N/A
ex vivo (excised tissues)	N/A	N/A	N/A	N/A
in vivo pre-clinical (lower-level organism or small animal)	N/A	N/A	N/A	N/A
in vivo pre-clinical (large animal)	N/A	N/A	N/A	N/A

Human subjects/clinical	Yes	No	The source data used for model validation is qualitative and the clinical protocols have been published in peer-reviewed journals	Adequate

Rule 3: Evaluate within context: Perform verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation with respect to the reality of interest and intended use(s) of the model or simulation.

Current Conformance Level: Extensive

	Who Does It?	**When does it happen?**	**How is it done?**	**Current Conformance Level**
Verification	Developer	During development	Comparison of model output with the experimental and clinical observations	Extensive
Validation	Lab Member	During development	model was used to reproduce simulations and figures	Extensive
Uncertainty Quantification	User performs uncertainty quantification	Can be performed every time the model is run for a new scenario	User discretion	Adequate
Sensitivity Analysis	User performs sensitivity analysis on influential parameters.	Can be performed after every new simulation	User discretion	Adequate

Rule 4: List limitations explicitly: Provide restrictions, constraints, or qualifications for or on the use of the model or simulation for consideration by the users or customers of a model or simulation.

Current Conformance Level: Comprehensive

Disclaimer statement (explain key limitations)	**Who needs to know about this disclaimer?**	**How is this disclaimer shared with that audience?**	**Current Conformance Level**
Models are limited by the spatial homogeneity approximation	Users	Stated in the main text	Comprehensive
Model does not capture metastasis and the associated transition and other necessary interactions	Users	Stated in the main text	Comprehensive
The conclusion drawn from this model are conditioned on the particular modeling rules specified in the main text	Users	Stated in the main text	Comprehensive

Rule 5: Use version control: Implement a system to trace the time history of modeling and simulation activities including delineation of each contributors' efforts.

Current Conformance Level: Extensive

	Naming Conventions?	**Repository?**	**Code Review?**
individual modeler	N/A	Github	Yes
within the lab	Yes	Yes	Yes
collaborators	N/A	Github	Yes

Rule 6: Document appropriately: Maintain up-to-date informative records of all modeling and simulation activities, including simulation code, model mark-up, scope and intended use of modeling and simulation activities, as well as users' and developers' guides.

Current Conformance Level: Extensive

	Current Conformance Level
Code Commented?	Extensive: Commented the codes in every important line of the code for better interpretability.
Scope and intended use described?	Extensive: Described in the beginning of the each section of the code and in the main text.
User's Guide	Extensive: described in the main text and supplemental files
Developer's Guide?	Adequate: Described in the main text and the supplementary files.

Rule 7: Disseminate broadly: Share all components of modeling and simulation activities, including simulation software, models, simulation scenarios and results.

Current Conformance Level: Extensive

Target Audience(s):	**"Inner Circle"**	**Scientific Community**	**Public**
Simulations			Description of simulations stated in the main text and supplemental files.
Models			Model files present in supplementary material and on GitHub.
Software			MATLAB
Results			Described in main manuscript and supplementary material
Implication of Results			Described in main manuscript.

Rule 8: Get independent reviews: Have the modeling and simulation activity reviewed by nonpartisan third-party users and developers.

Current Conformance Level: Extensive

Reviewer(s) name and affiliation	**Shaina Robbins (Thomas Jefferson University)**
When was the review performed?	August 15, 2024
How was review performed and outcomes of the review?	1. A member of the research group, not involved in the present study and does not conduct research in tumor microenvironment modeling, performed the review. Model scripts were cross-checked for consistency. Simulation results and figures were independently reproduced using the files provided on GitHub. 2. A member in the previous lab of the first author of this manuscript, not involved in modelling the TME, independently created the model from the equations described in the supplementary material and successfully reproduced Fig. 3 of the main manuscript.

Rule 9: Test competing implementations: Use contrasting modeling and simulation implementation strategies to check the conclusions of different strategies against each other.

Current Conformance Level: Adequate

	Yes or No (briefly summarize)
Were competing implementations tested?	Competing implementations were conceptualized by all the authors and tested by the first author of this manuscript.
Did this lead to model refinement or improvement?	Yes, the completing implementations led to modifications and refinements of the model.

Rule 10: Conform to standards: Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and regulations accepted as best practices.

Current Conformance Level: Adequate

	Yes or No (briefly summarize)
Are there operating procedures, guidelines, or standards for this type of multiscale modeling?	Yes, Erdemir *et al.* (2020) proposed a set of well-define rules to assess the credibility of computational models in healthcare [1].
How do your modeling efforts conform?	The proposed model was implemented in MATLAB 2022B, a widely used software for computational and mathematical analysis. We used the stiff ordinary differential equation solver- ode23s in MATLAB to simulate the computational model.

References:

1. Erdemir, A.; Mulugeta, L.; Ku, J.P.; Drach, A.; Horner, M.; Morrison, T.M.; Peng, G.C.Y.; Vadigepalli, R.; Lytton, W.W.; Myers, J.G. Credible Practice of Modeling and Simulation in Healthcare: Ten Rules from a Multidisciplinary Perspective. *J. Transl. Med.* **2020**, *18*, 369, doi:10.1186/s12967-020-02540-4.