# Using Information from the Microbiome to Improve the Efficiency of Diagnostic-Therapeutic Options for Melanoma: A Cost-Effectiveness Analysis

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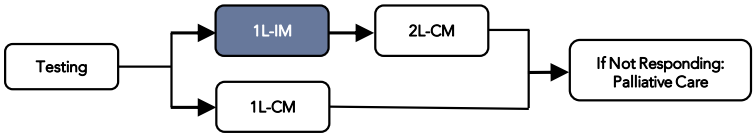
## I. IMPORTANCE AND OBJECTIVE OF THE STUDY

- Composition and diversity of the patient's gut microbiome play a growingly pivotal role in determining the efficiency of immunotherapies. Gut microbiome test (GMT) could potentially be valuable to guide clinical and patient decision making in oncology treatments; however the cost and effectiveness value of such efforts are unknown.
- This study evaluates the cost-effectiveness of adding a gut microbiome test (GMT) to the routine PD-L1 testing to guide treatment choice between immunotherapy and chemotherapy options in the care of patients with metastatic or unresectable cancer.

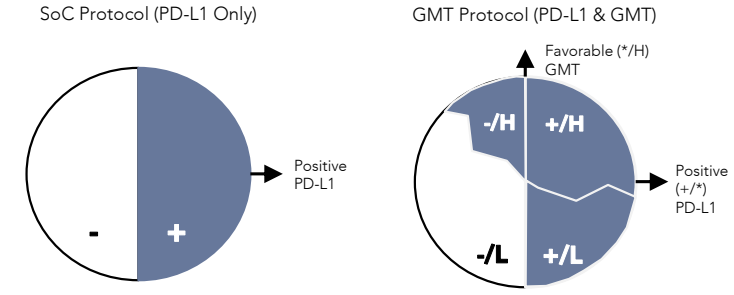
## II. MODEL OVERVIEW

- Decision tree model from the public perspective with targeted patient population of Medicare enrollees (assuming avg. age 65) that are diagnosed with metastatic or unresectable melanoma.
- Standard-of-Care (SoC) uses PD-L1 testing only for treatment decision making. GMT protocol determines treatment based on results of both PD-L1 test of tumor and GMT result of stool.
- First-line Immunotherapy (1L-IM) uses combination of nivolumab and ipilimumab and is based on settings in clinical trials *CheckMate066* and *CheckMate 067*. Cytotoxic chemotherapy, both first-line (1L-CM) and second-line (2L-CM), uses FDA approved treatment for melanoma, Dacarbazine. Palliative care is used when patient does not respond to treatments.
- Distilled model diagrams below illustrates the building blocks of the model design.

**Flowchart on Diagnostic-Therapeutic Decisions of Melanoma Patients**




**GMT Guided Change on Who to Receive Immunotherapy**




*For illustration purposes only and area does not represent actual model input.*

## III. MODEL DETAILS

- Micro-costing data sourced from national surveys and published literature. Treatment responding probabilities given known testing results are derived using hazard functions, and hazard ratios (HR) are assumed using lognormal dist. for multivariate sensitivity analysis (PSA). For other parameter categories, Beta dist. is assumed for probability and utility, Gamma dist. is assumed for cost, and normal dist. is assumed for life expectancies.

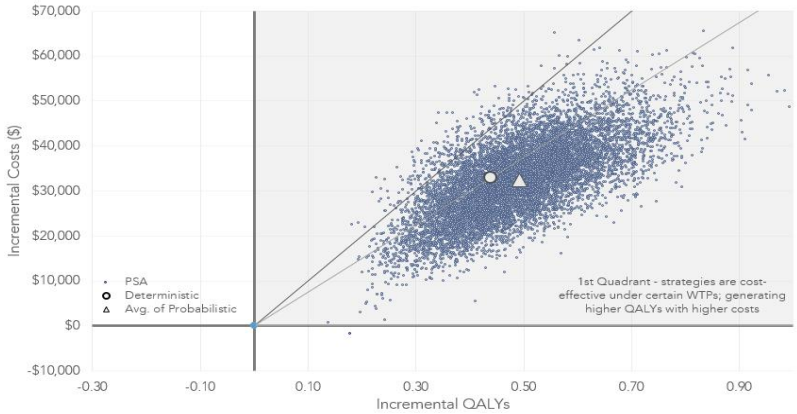
| KEY PARAMETERS | BASELINE VALUE | REFERENCE |
|---|---|---|
| **PROBABILITY** | | |
| Positive PD-L1 | 0.25 | Wolchok et al., 2017 |
| Favorable GMT given positive PD-L1 | 0.6 | Assumption |
| Favorable GMT given negative PD-L1 | 0.4 | Assumption |
| Responding to IM given positive PD-L1 | 0.72 | Larkin et al., 2015 |
| Responding to IM given negative PD-L1 | 0.55 | Larkin et al., 2015 |
| Responding to IM given (+ / H) | 0.9 | Calculation per HR |
| Responding to IM given (- / H) | 0.81 | Calculation per HR |
| Responding to CM | 0.15 | Lui et al., 2007 |
| Responding to CM given favorable GMT | 0.17 | Calculation |
| Responding to CM given unfavorable GMT | 0.14 | Calculation |
| **COST (ADJUSTED TO 2019 USD)** | | |
| PD-L1 Testing Cost | $142.75 | CMS |
| GMT Cost | $70.00 | Maas, 2015 |
| First-line Immunotherapy Cost | $169,887.47 | Calculation |
| First-line Chemotherapy Cost | $1,037.84 | Calculation |
| Second-line Chemotherapy Cost | $11,320.98 | Calculation |
| **UTILITY AND LIFE EXPECTANCY** | | |
| Baseline receiving IM | 0.79 | Tarhini et al., 2019 |
| Baseline receiving CM | 0.69 | Shih et al., 2015 |
| Utility of progressed disease or nonresponding | 0.52 | Tringale et al., 2017 |
| Disutility of Experiencing AEs caused by IM or CM | 0.13 | Tarhini et al., 2019 |
| Overall survival length for IM | 3.10 | Wolchok et al., 2017 |
| Overall survival length for CM | 0.93 | Prigerson et al., 2015 |

## IV. FINDINGS AND IMPLICATIONS

- The addition of microbiome testing on routine PD-L1 testing may provide economic and clinical value in the care treatment paradigm of metastatic or unresectable melanoma. It is considered a cost-effective strategy with willingness-to-pay threshold of $75,000-$100,000 per QALY. The 95% credible interval for the ICER generated using Monte Carlo simulations shows the same conclusion.
- Our research points out future study directions on utilizing Real World Evidence to further elucidate and quantify the efficiency and responsiveness of cancer patients with favorable microbiome indicators.

**Cost-Effectiveness Plane with Deterministic and Probabilistic Results**

10,000 Trials of Monte-Carlo Simulation




**Univariate Analysis on Impact to ICER of GMT Protocol**

| | 25% Lower | 25% Higher |
|---|---|---|
| Costs of IM | $55,516 / QALY | $94,942 / QALY |
| Probability of having favorable GMT given positive PD-L1 | $72,088 / QALY | $77,567 / QALY |
| Probability of having favorable GMT given negative PD-L1 | $64,115 / QALY | $81,630 / QALY |
| IM responding rate given positive PD-L1 | $65,148 / QALY | $90,492 / QALY |
| Life expectancy of patients respond to IM | $104,319 / QALY | $58,825 / QALY |

***All references available upon request.***