Beyond PD-L1: Challenges in Implementing Tumor Mutational Burden (TMB) to Predict Patient Response to Immuno-Oncology (I-O) therapies.

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Introduction:

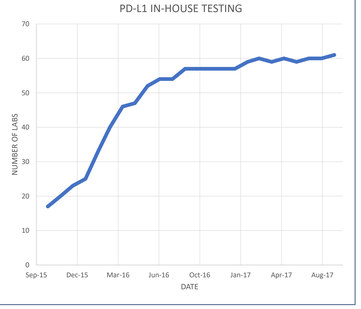
Tumor Mutational Burden (TMB) is a representation of the number of mutations in a tumor genome providing a measure of accumulated genomic damage in tumors. High TMB has been shown to be predictive of patient response to immuno-oncology (I-O) therapy in many solid tumors and is currently being investigated in clinical studies for its ability to stratify patients for I-O therapy. PD-L1 is widely used to predict patient response to I-O therapy despite challenges due to variable expression levels and poor correlation to therapeutic response. To determine real-world laboratory readiness for TMB adoption, we investigated current laboratory test menus, geographic distribution, testing capabilities and new test adoption behaviors of clinical laboratories across the U.S.

Methods:

Diaceutics maintains and continually grows a database of Global diagnostic testing labs. The database is a partnership driven collection of laboratory data including test offerings, methodologies, sample and test volumes, turn-around time and test capabilities. Diaceutics additionally tracks laboratory behaviors that influence new test adoption. We collected and analyzed information from our Database, as well as through secondary market research and discussions with laboratory partners from clinical labs across the U.S. to determine current Next Generation Sequencing (NGS) capabilities and current TMB landscape. We have identified the labs currently offering clinical NGS, trends in NGS adoption and labs who may be able to offer TMB in the near term. We have also used historical datasets to analyze factors likely to influence future TMB adoption.

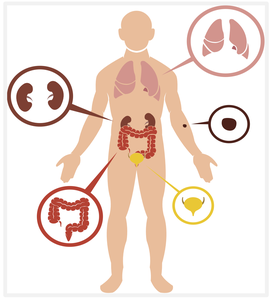
PD-L1 Test Adoption in the US

- Adoption of PD-L1 testing by Immunohistchemistry rapidly followed companion and complementary diagnostic label approvals.
- Howevever the number of laboratories quickly plateaued around 60 labs in the us offering testing
- We hypothesize market confusion lead to an early plateau of PD-L1 adoption
  - Multiple antibody clones
  - Challenging Interpretation
  - Companion vs Complementary label



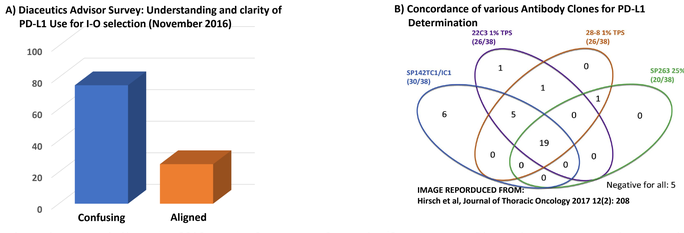
TMB a new biomarker for I-O Selection?

- Tumor Mutation Burden (TMB) refers to the total absolute number of mutations found in a tumor genome
- High TMB has been correlated with increased recognition of the tumor by immune cells via MHC class I presentation of high neoantigen expression[1,2]
- High TMB has been shown to predict I-O response in several tumor types:
  - Lung cancer[3]
  - Colorectal cancer[4]
  - Bladder cancer[5]
  - Melanoma[6]
  - Renal cell carcinoma[7]
- **TMB is currently being investigated in numerous clinical trials as a biomarker for I-O selection**



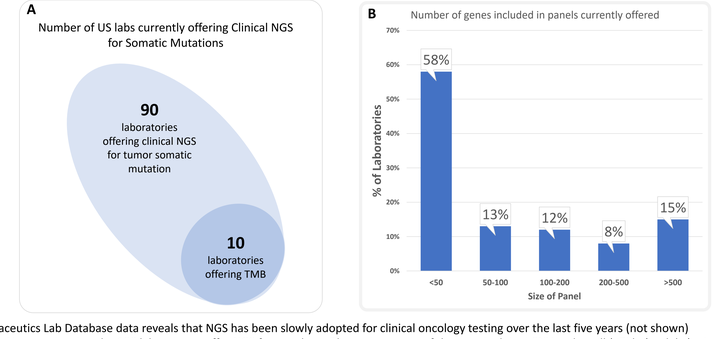
[1]http://science.sciencemag.org/content/348/6230/69 [2]https://www.omicsonline.org/open-access/cancer-neoantigens-a-promising-source-of-immunogens-for-cancer-immunotherapy-2155-9899-1000322.php?aid=52360 [3]http://science.sciencemag.org/content/348/6230/124 [4]http://www.nejm.org/doi/full/10.1056/nejmoa1500596 [5]http://dx.doi.org/10.1016/S0140-6736(16)00561-4 [6]http://www.nejm.org/doi/full/10.1056/NEJMoa1406498 [7]http://meetinglibrary.asco.org/content/156995-172

PD-L1 an imperfect biomarker; poorly executed



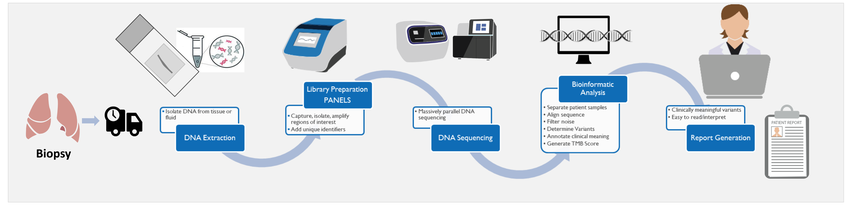
A) A Diaceutics advisor survey in November 2016 revealed 2 years post- Companion/Complementary Diagnostic launch, pathologists were still largely unclear on the use and value of PD-L1 as a biomarker.
B) Concordance study was performed and published nearly three years after PD-L1 first appeared in a therapeutic drug label

NGS Test Adoption in the US



Diaceutics Lab Database data reveals that NGS has been slowly adopted for clinical oncology testing over the last five years (not shown)
A) At present just under 100 laboratories offer NGS for oncology. The vast majority of these tests detect SNV and small (<70bp) indels (not shown)
B) Nearly 50% of somatic NGS testing is using small gene panels or hotspot panels at this time (Q3 2017)
Nagarajan et al (Arch Pathol Lab Med. 2017) recently published results from CAP survey with similar NGS data

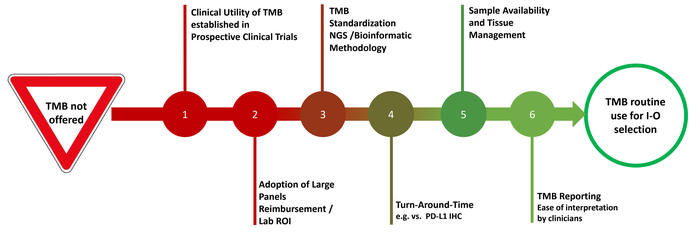
Complex NGS workflow presents challenge for TMB standardization



Examples of Key Technical Considerations for TMB

- **Gene number / genomic coverage:** impact be on clinical accuracy of TMB
- **Genes / Genomic regions:** impact of genomic area, genes included on TMB result?
- **Bioinformatics: Filtering methods:** potential to greatly change variation called
- **Bioinformatics: genomic alterations included in TMB scoring:** impact TMB scoring
- **Bioinformatics: TMB cut-off calculations** potential to normalize to different methods and tissues
- **Reporting:** Standardized way to report TMB result

Key Barriers to TMB Adoption in the US for I-O selection



Diaceutics has identified six key barriers to successful TMB adoption

- Barriers are derived from current database, advisor feedback and extrapolating past companion/complementary diagnostic test launch
- **Laboratory methods concordance studies will be key prior to use of TMB for I-O patient selection**

Conclusion:

Tumor Mutational Burden (TMB) has the potential to be a useful test for I-O patient selection. The requirement for large gene panels/genomic coverage for TMB may drive comprehensive genomic profiling for subsets of patients by providing all mutations and alterations in a single test along with TMB for I-O selection. Molecular pathology labs and pathologists have the opportunity to study the effects of method variation on TMB reporting and standardize TMB thereby avoiding much of the confusion suffered with PD-L1 immunohistochemistry. Clinical utility and Payer adoption are the top barriers for TMB adoption in the US market.