Alignment of TMB measured on clinical samples: Phase 2B of the Friends of Cancer Research TMB Harmonization Project

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Disclosure of Relevant Financial Relationships

I have no relevant financial relationships to disclose

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Tumor Mutational Burden (TMB)

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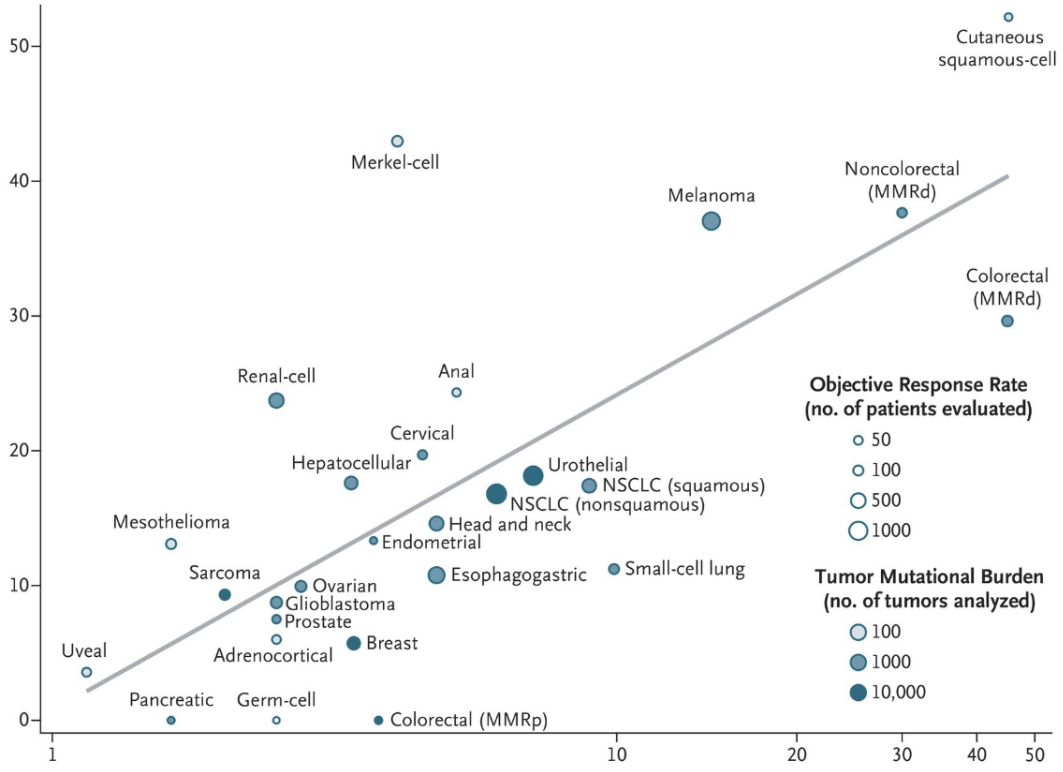
- A measure of the number of somatic mutations per area of the tumor's genome (mut/Mb)
- High TMB occurs in numerous tumor types and evidence is growing for the association of TMB with neoantigen load [1]
- TMB is a predictive biomarker and has been shown to correlate with clinical benefit from cancer immunotherapies [1,2]
- Methods of TMB estimation and reporting vary widely across clinical studies[3]

Correlation between TMB and ORR with anti-PD-L1/PD-1 therapy in 27 tumor types[4]



1. Chan TA, et al. *Ann Oncol*. 2019. 2. Chalmers ZR, et al. *Genome Med.* 2017. 3. Stenzinger A, Allen JD, et al. *Genes Chromosomes Cancer*. 2019. 4. Yarchoan M, et al. *N Engl J Med.* 2017.

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Friends of Cancer Research TMB Harmonization Project

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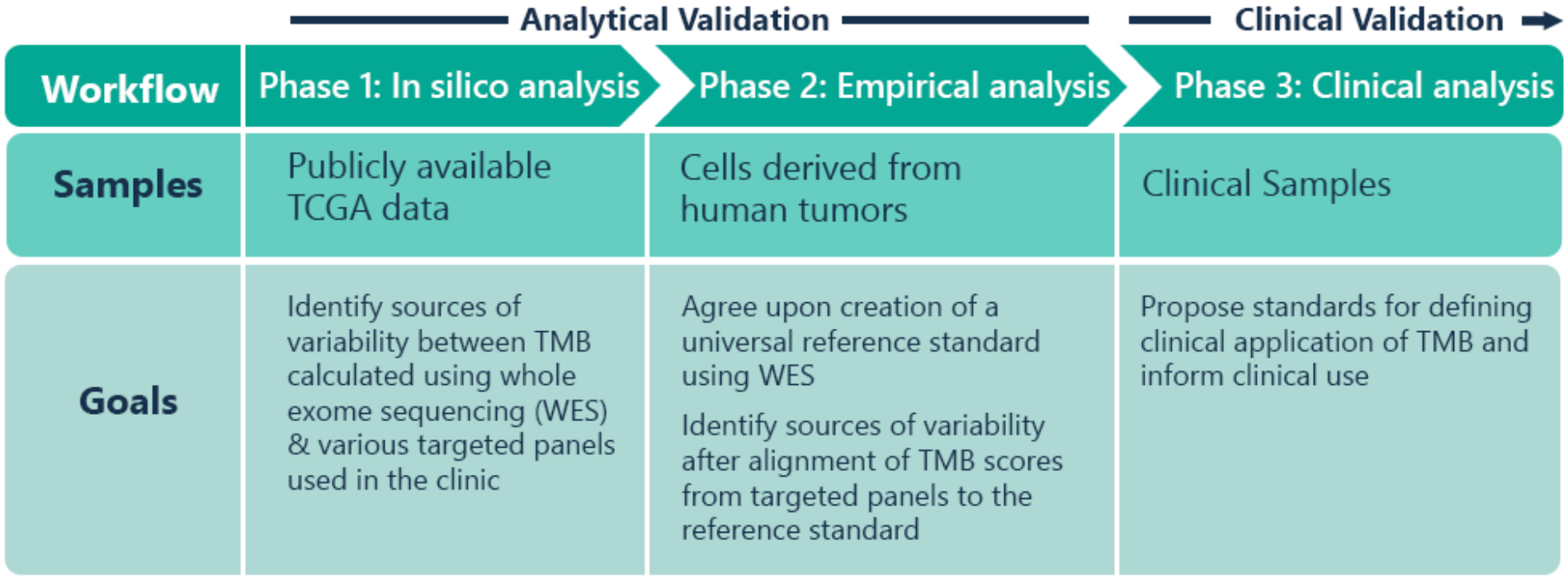
Multi-stakeholder working group to align on and publish universal best practices for defining TMB, and analytic validation approaches including alignment against reference standards.



Merino et al. *J Immunotherapy Cancer*, 2020

www.focr.org/tmb

Phase 2B: Empirical Analysis- Clinical Samples

Clinical Samples

25 tumor-normal matched FFPE clinical samples

DNA extracted in reference lab

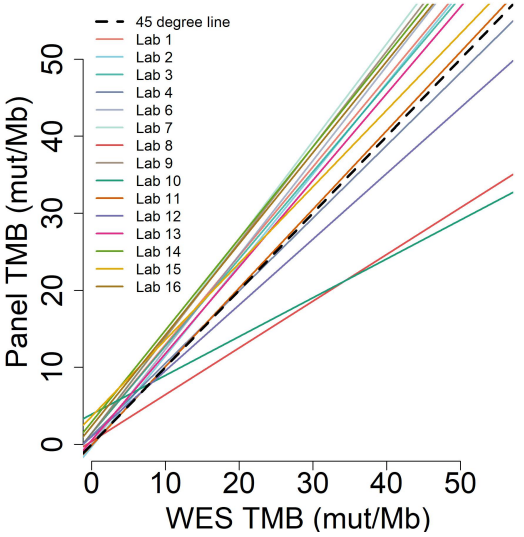
Different cancer types (lung, bladder, gastric)

Clinical samples WES → Consortium agreed TMB algorithm → Clinical samples WES-TMB score

Clinical samples NGS panel → Lab TMB algorithm → Panel TMB score

Assessing empirical variability in WES TMB vs. panel TMB

1



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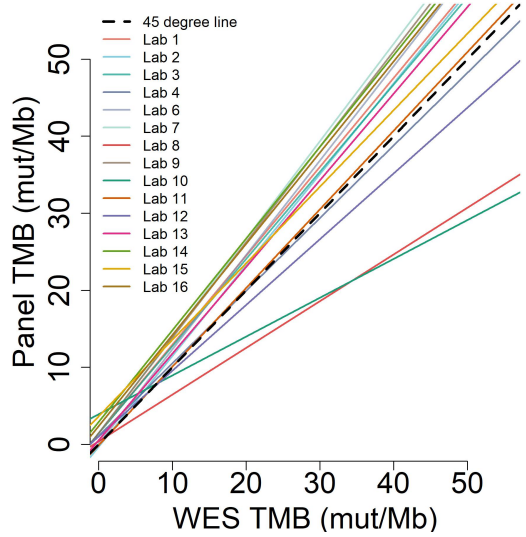
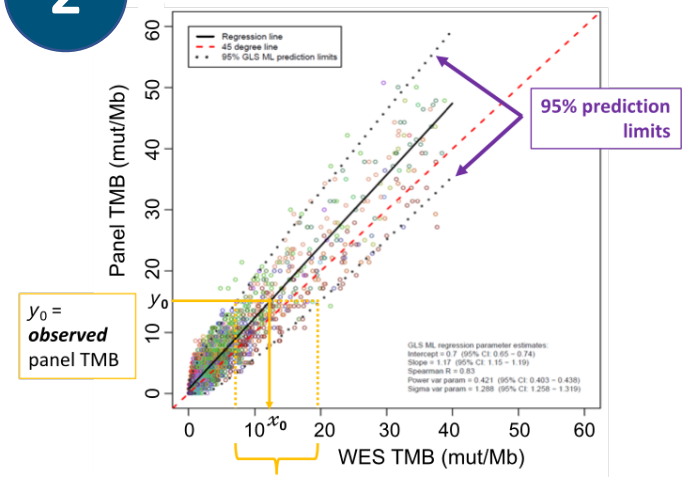


3 calibration methods

Clinical Samples NGS panel →
- All TCGA WES vs. panel
- Stratum 1 TCGA WES vs. panel
- Cell line WES vs. panel

Apply calibration approaches to align across NGS panels

2



x_0 = ***estimated*** *WES TMB calculated from calibration curve* at observed y_0
$(CLL_{95}(y_0), CUL_{95}(y_0))$ = interval of uncertainty around x_0

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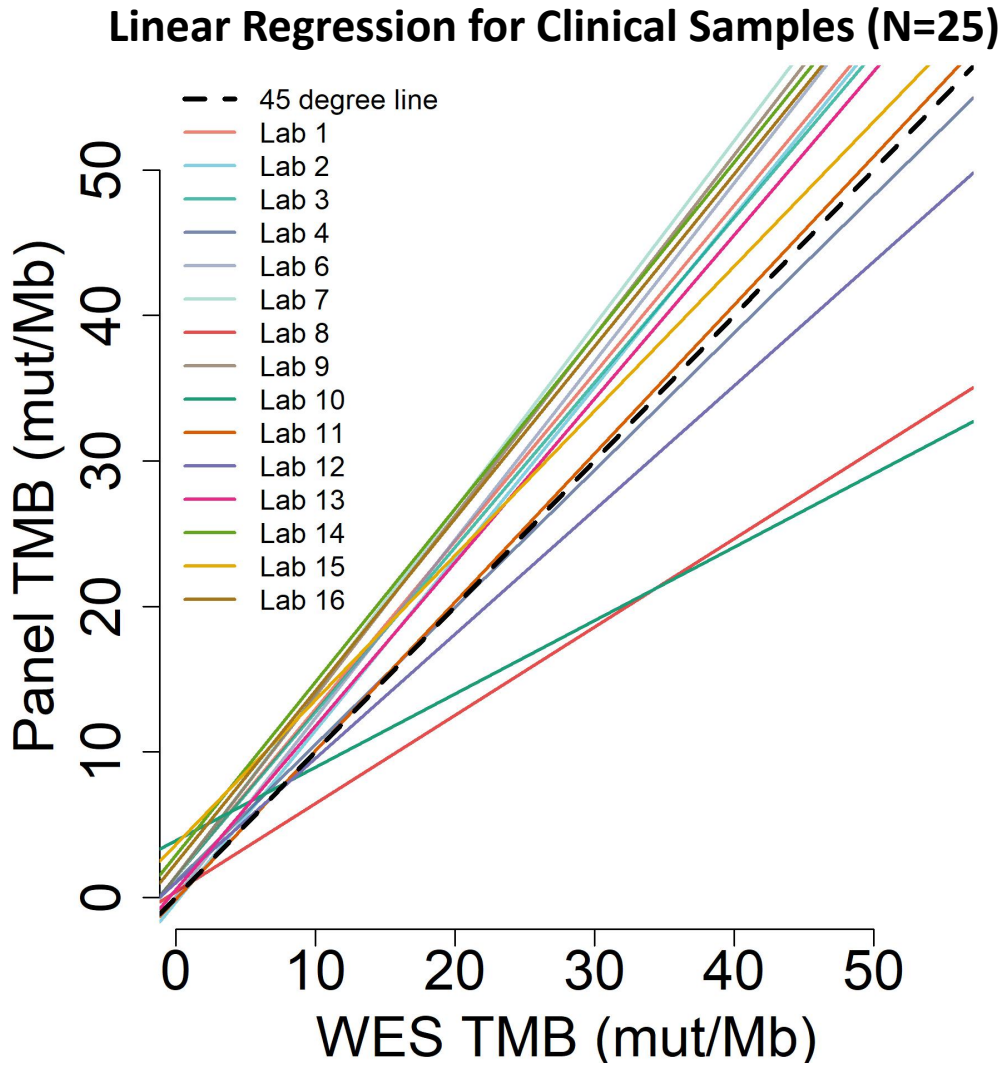
Variability in estimated association between panel TMB and WES TMB across participating laboratories



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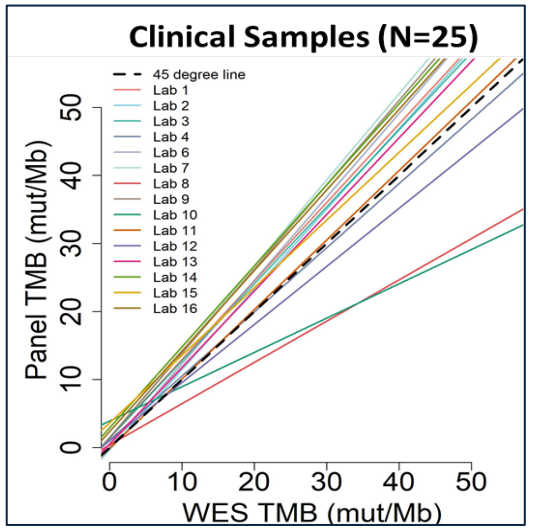
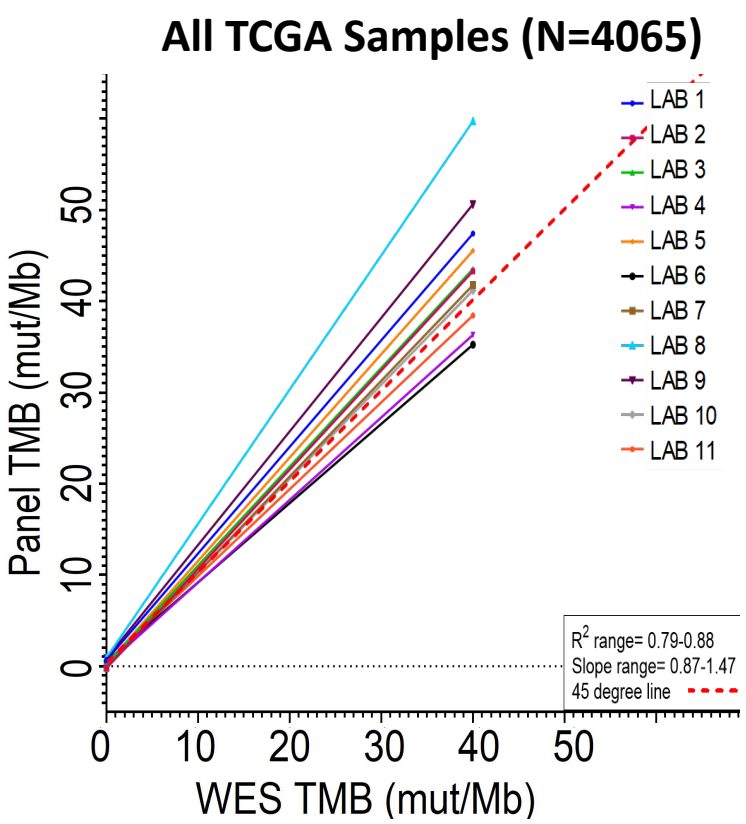
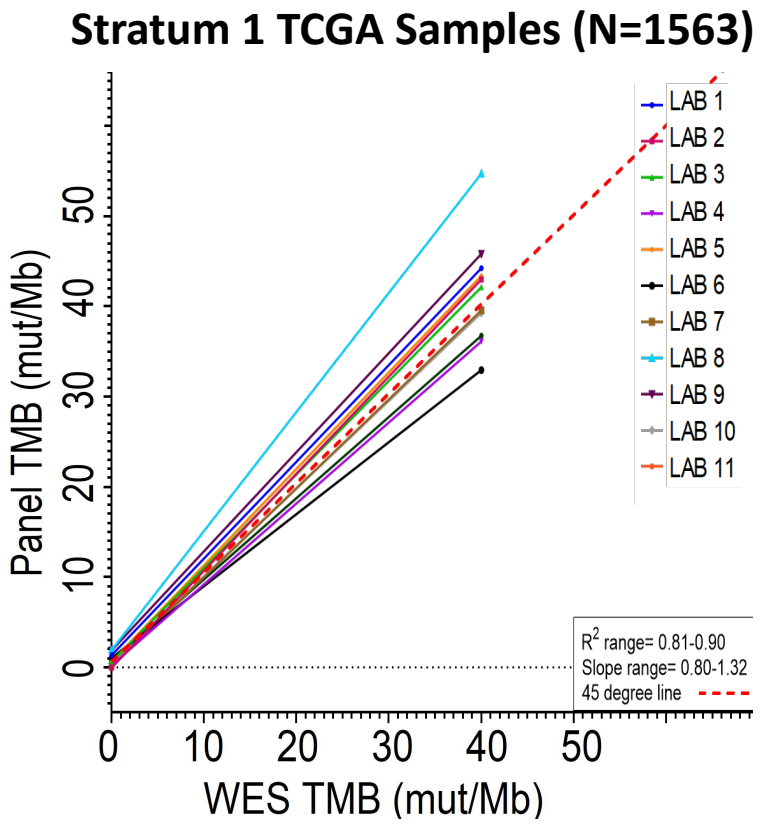
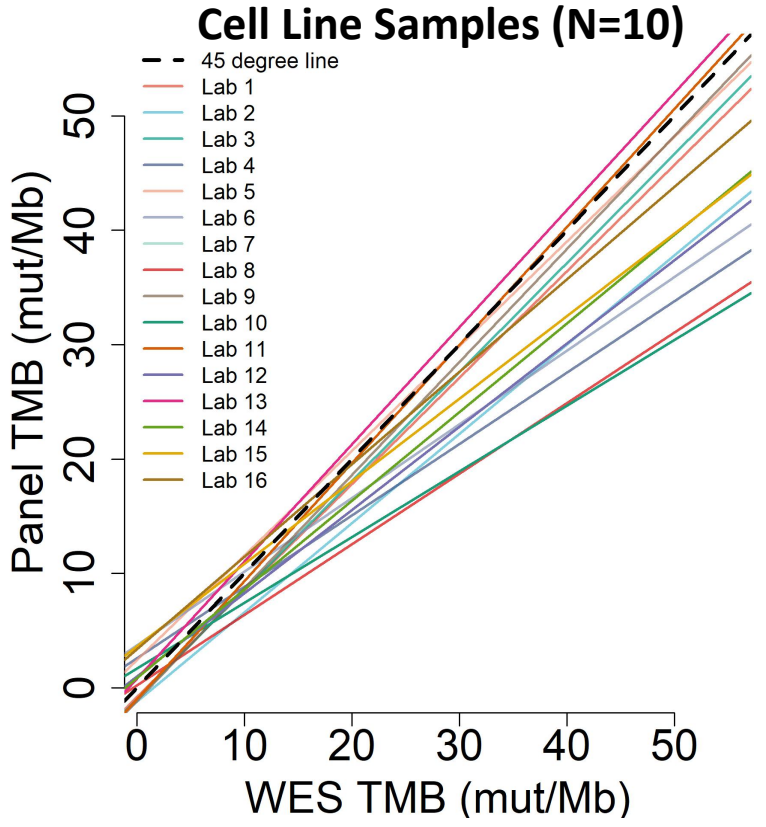
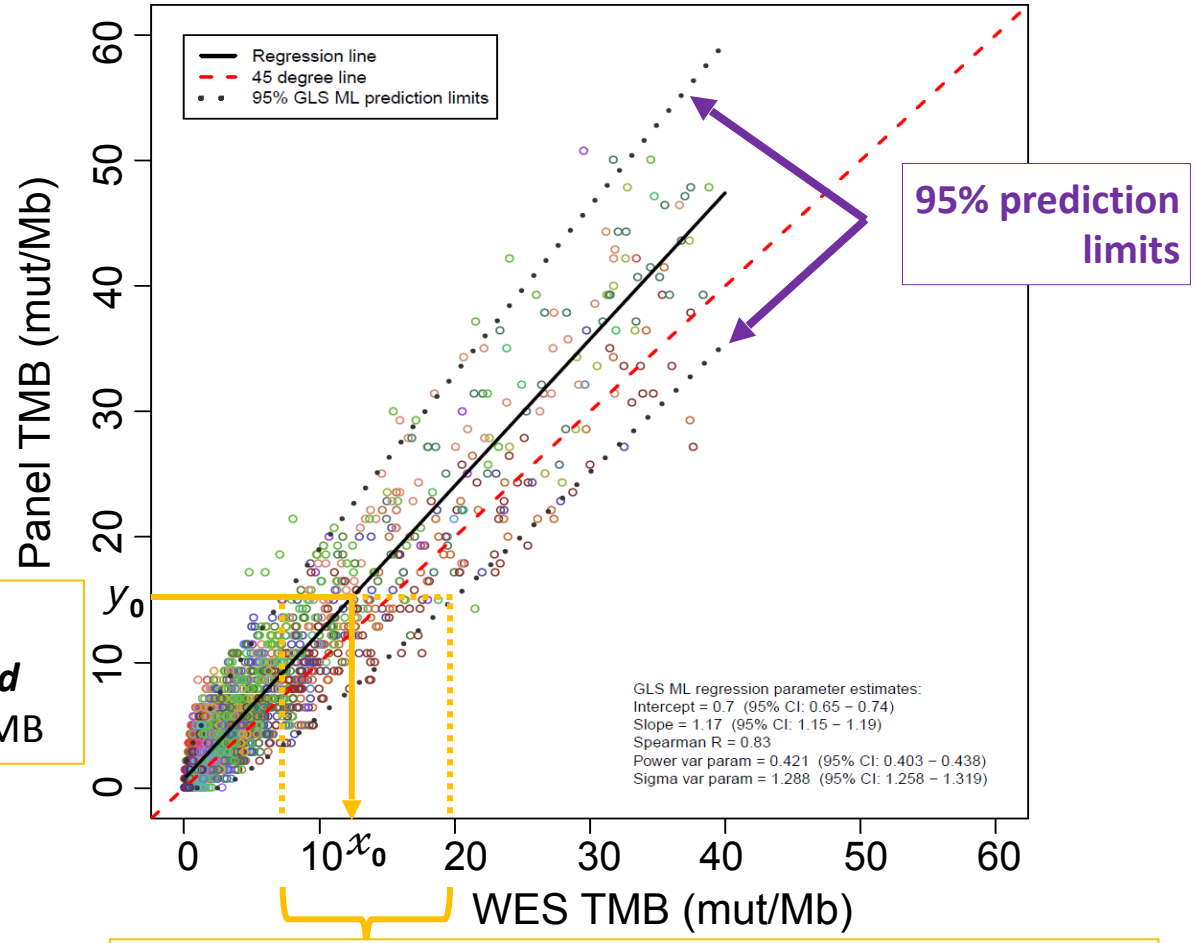








Calibration approaches using TCGA & cell lines as reference standards



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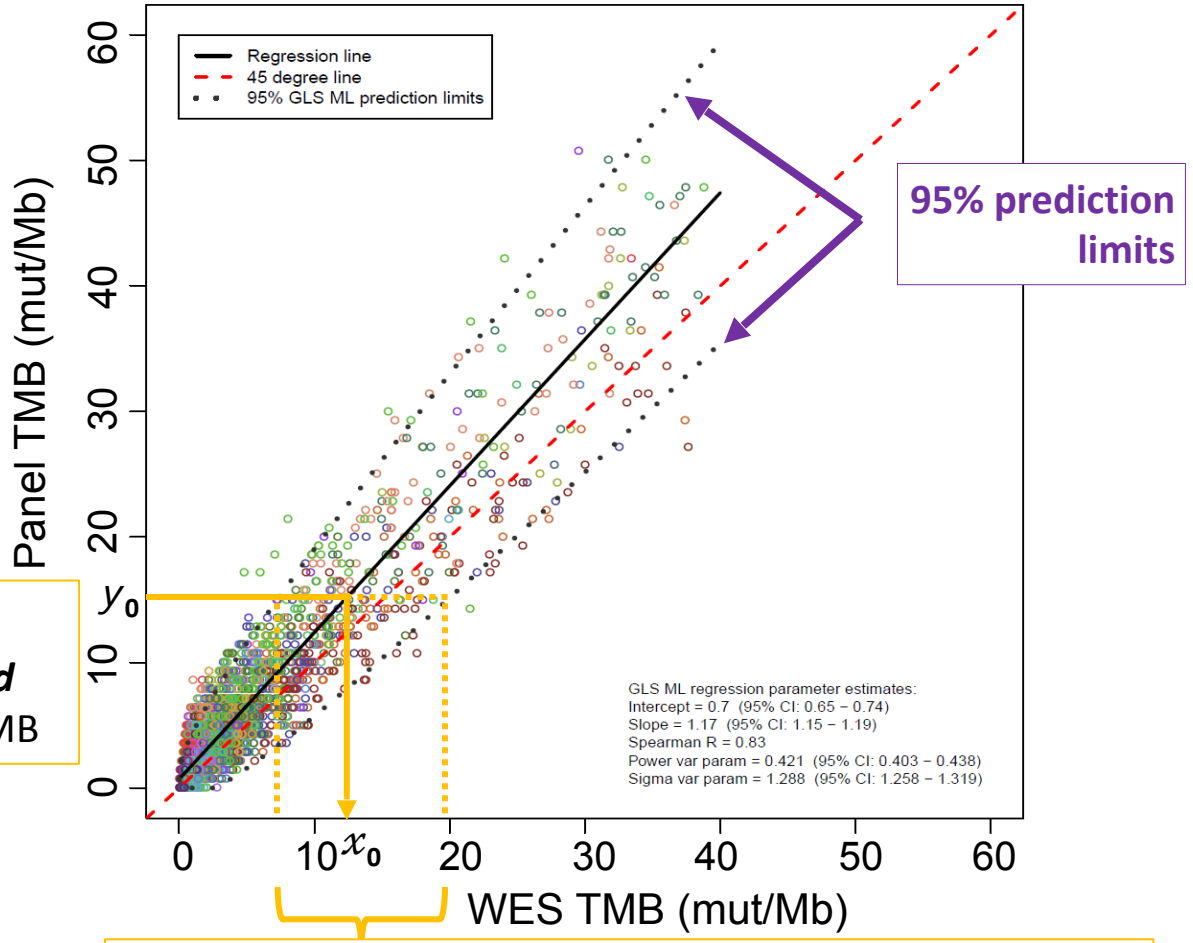

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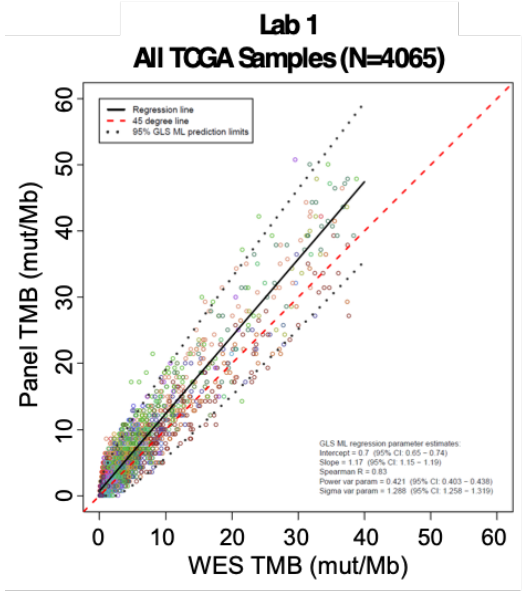

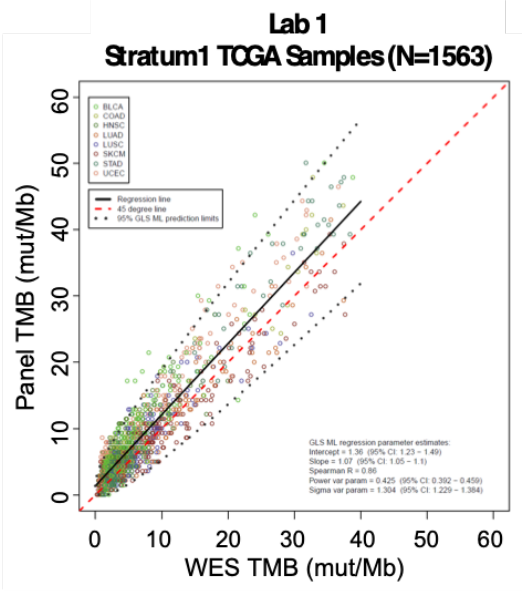

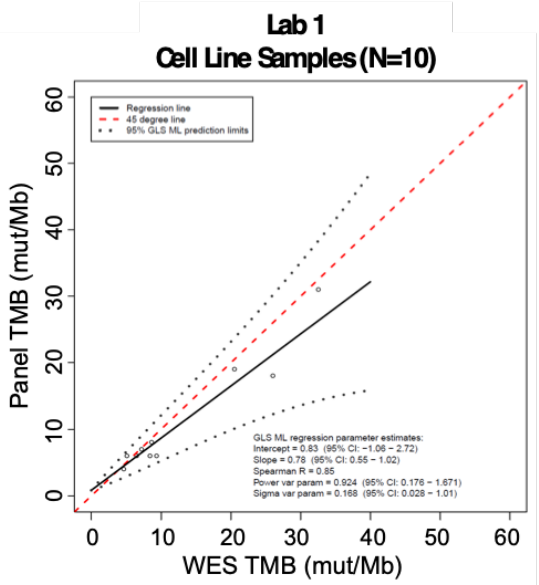

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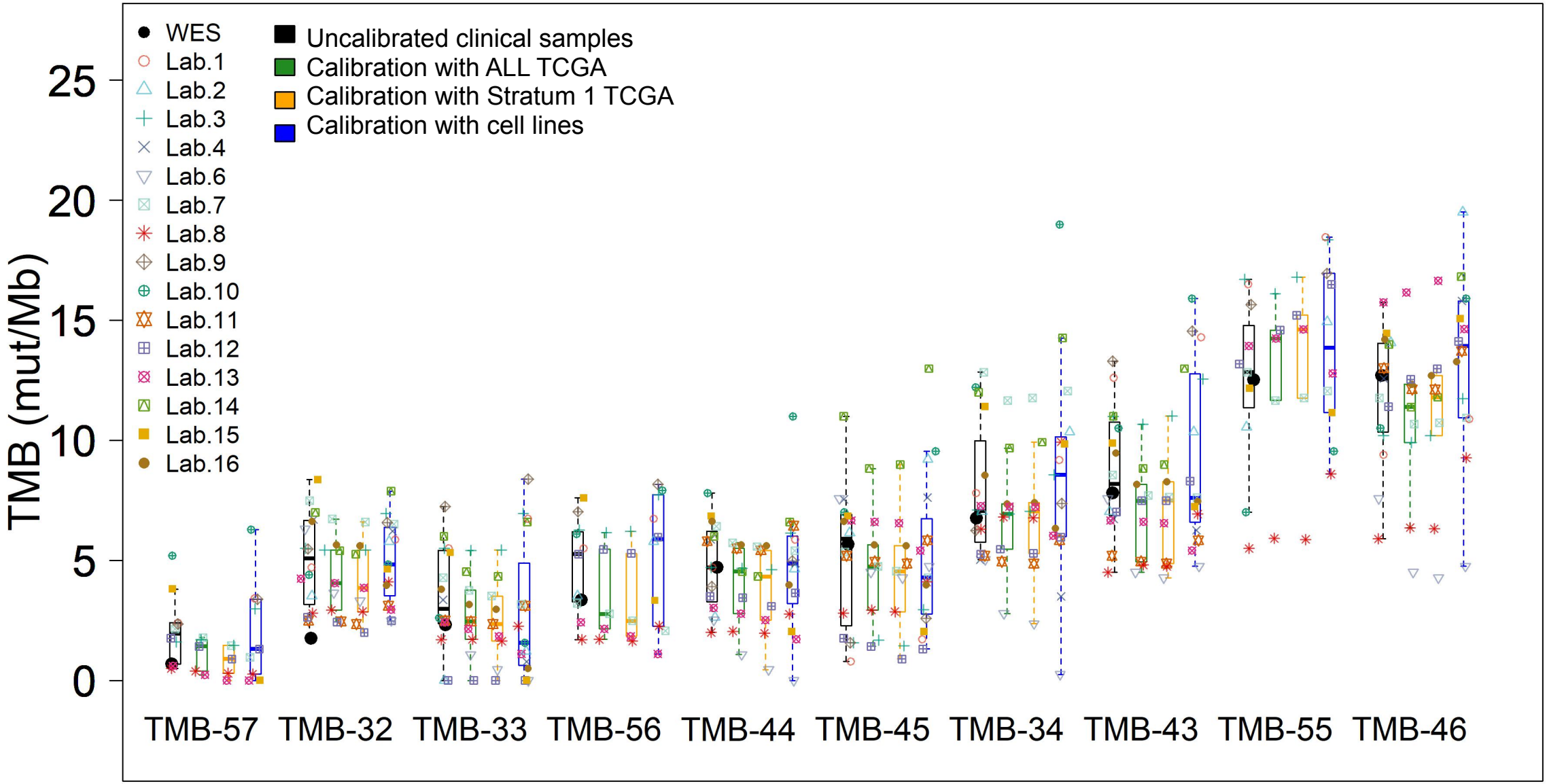
Application of Three Calibration Approaches to Lung Clinical Samples (N=10)



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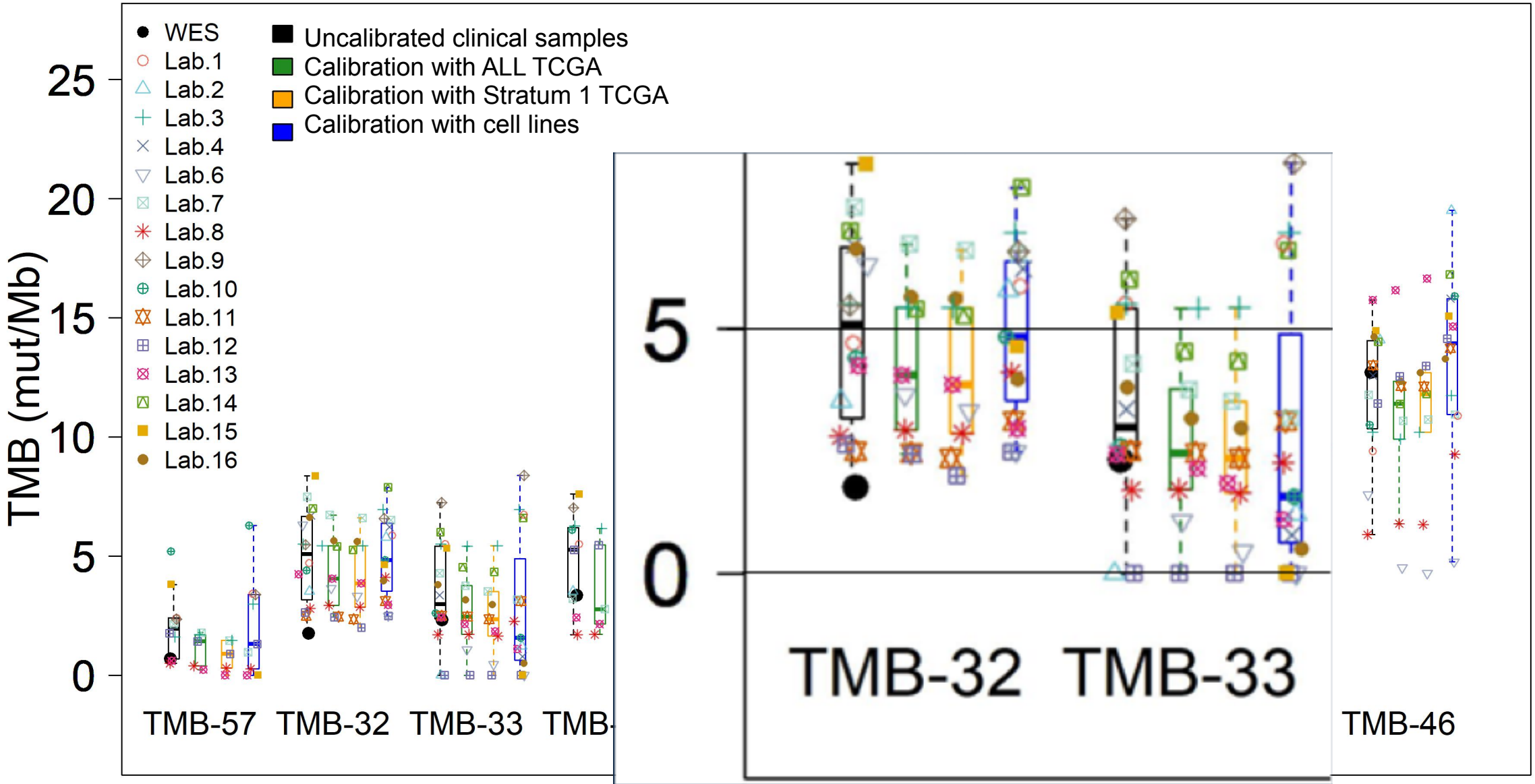

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Phase 2B: Summary of Findings

- Variability in the association between panel TMB and WES TMB across participating laboratories when testing FFPE-derived tumor samples was similar to that observed in TCGA samples and cell lines.
- Calibration approaches using TCGA data were more robust than those using a relatively small number of cell line samples, minimizing the spread in panel TMB values for clinical samples
- Calibration methods using TCGA may be a viable approach to align across panel TMB scores
- Ongoing work will explore whether TCGA calibration methods perform consistently in additional tumor samples, including TMB-high samples

Friends TMB Harmonization Project Catalyzing Change Through Collaboration

- Convening stakeholders early in the development of complex diagnostics will help identify key challenges and streamline measures to solve them
- Collaborative approach is necessary to improve consistency and reliability of panel TMB estimates to be used in the clinic
- Scientific and regulatory approaches are necessary for alignment on optimal performance thresholds and standards development

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TMB Harmonization Consortium

Government: National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA) **Academia:** Brigham & Women's Hospital, College of American Pathologists (CAP), Columbia University, EORTC, Genomic Testing Cooperative, Hartwig Medical Foundation, Johns Hopkins University, Massachusetts General Hospital, MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Quality in Pathology (QuIP), University of Heidelberg **Diagnostics:** ACT Genomics, Biodesix, Caris Life Sciences, Foundation Medicine, Inc., Guardant Health, Inc., Illumina, Inc., Intermountain Precision Genomics, NeoGenomics Laboratories, Inc., OmniSeq, Personal Genome Diagnostics (PGDx), Q^2 Solutions, QIAGEN, Inc., Quest Diagnostics, RocheDx, Thermo Fisher Scientific, Thrive **Industry:** AstraZeneca, Bristol-Myers Squibb Company, EMD Serono, Inc., Genentech, Merck & Co., Inc., Pfizer, Inc., Regeneron Pharmaceuticals **Operational:** precisionFDA, SeraCare

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Thank you!

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focr.org/tmb

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