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Society for Immunotherapy of Cancer

TMB Harmonization Project

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President & CEO
Friends of Cancer Research

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Financial Disclosures

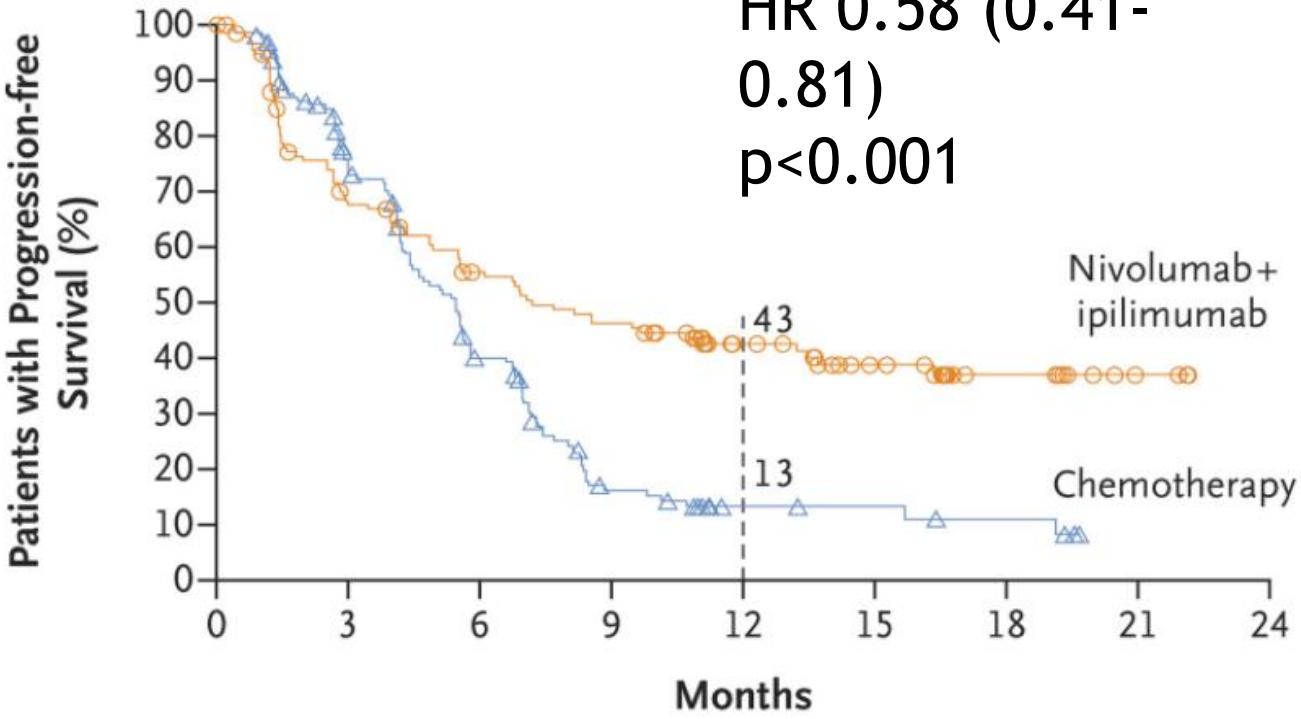
- I have no disclosures to report.
- Funding for this project has been provided by the participants who have performed their individual TMB analyses.

FRIENDS of CANCER RESEARCH

TMB is predictive, not prognostic

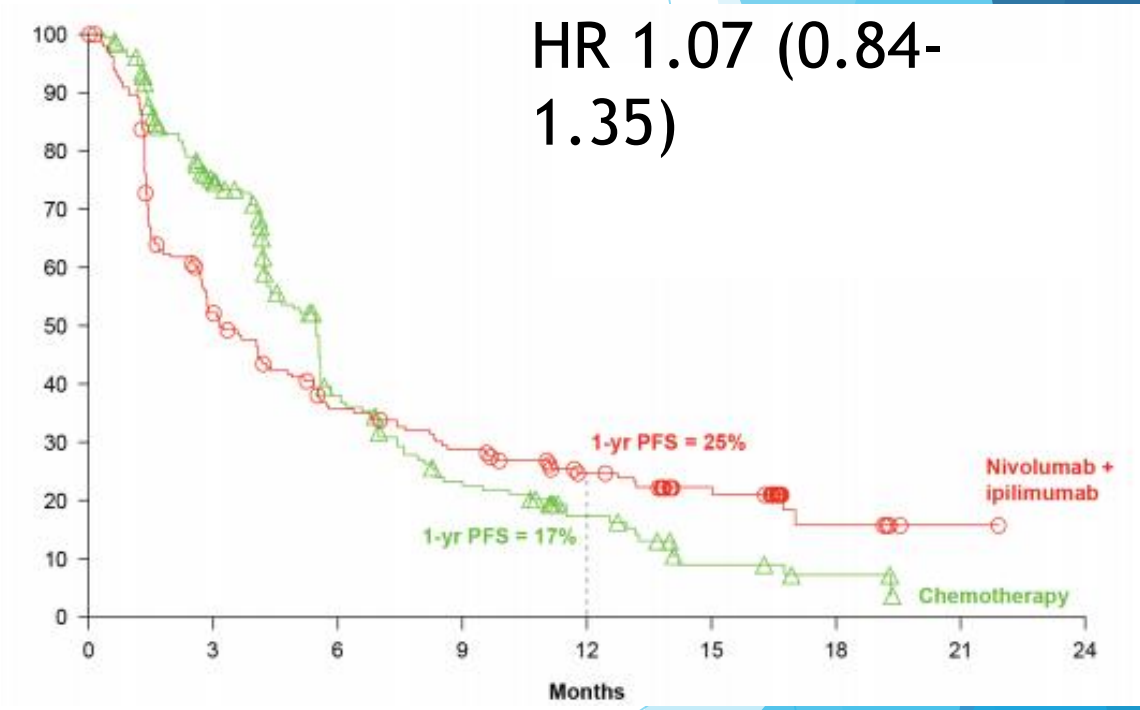
TMB high

HR 0.58 (0.41-0.81)
p<0.001



TMB low

HR 1.07 (0.84-1.35)



***Predictive not prognostic*: The positive association between TMB and outcome is limited to immunotherapy.**

Hellmann, NEJM 2018

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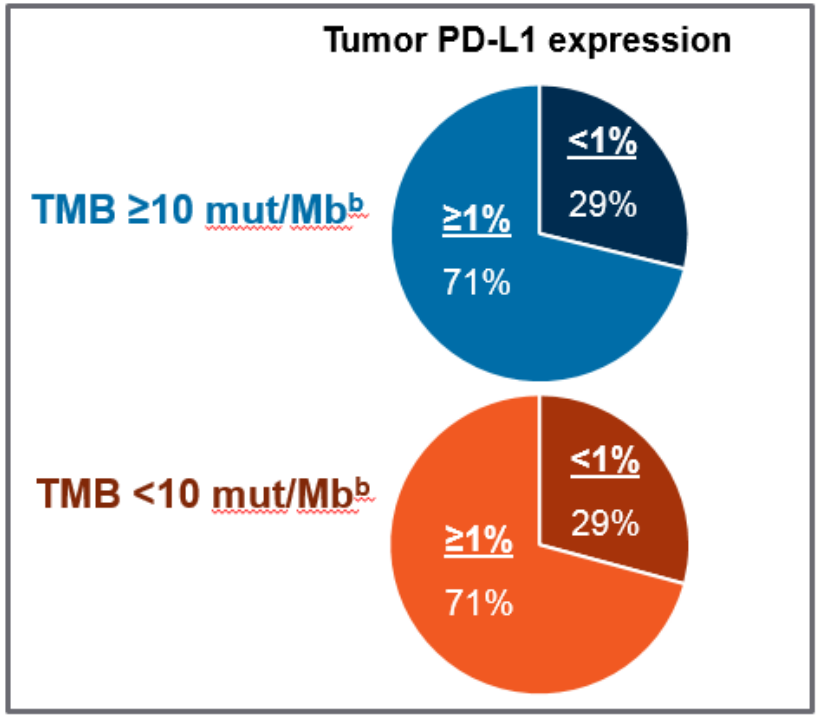
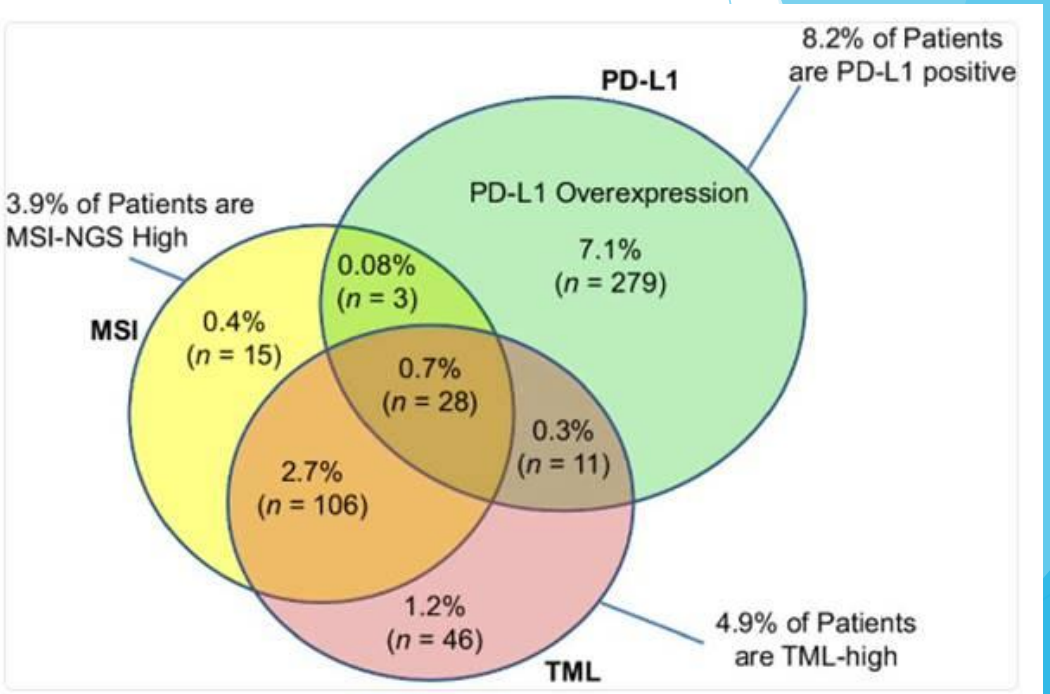
TMB is an independent biomarker





***Orthogonal, not overlapping*: Mutation burden is independent of other predictive variables (PDL1, MSI, GEP)**

Hellmann, NEJM 2018
Salem, Mol Cancer Res 2018

Need for Standardizing TMB Assessment

- Interest in TMB assessment as a biomarker for response to immune checkpoint inhibitors is increasing
  - The number of published studies and studies registered in the ClinicalTrials.gov database has increased over recent years[1]
    - 98 trials registered as of March 2019

- Methods of TMB estimation and reporting vary widely across clinical studies[2-5]
  - **Assays:** whole exome sequencing (WES) and various targeted gene panels
  - **Parameters:** sample type, genome coverage, genomic considerations, bioinformatics pipelines, cutoff values, and reporting methods

- Reliable TMB measurement is critical for consistent identification of patients who are likely to benefit from immune checkpoint inhibitors[5-7]

1. NIH. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/home. Accessed March 2019. 2. Chalmers ZR, et al. *Genome Med* 2017;9:34. 3. Hellmann MD, et al. *N Engl J Med* 2018;378: 2093–2104. 4. Velcheti V, et al. *J Clin Oncol* 2018;36(suppl 15). Abstract 12001. 5. Chang H, et al. *Ann Oncol* 2018;29(suppl 8):viii14-viii57. 6. Chen H, et al. *Cancers (Basel)* 2015;7:1699–1715. 7. Deans ZC, et al. *Virchows Archiv* 2017;470:5–20.

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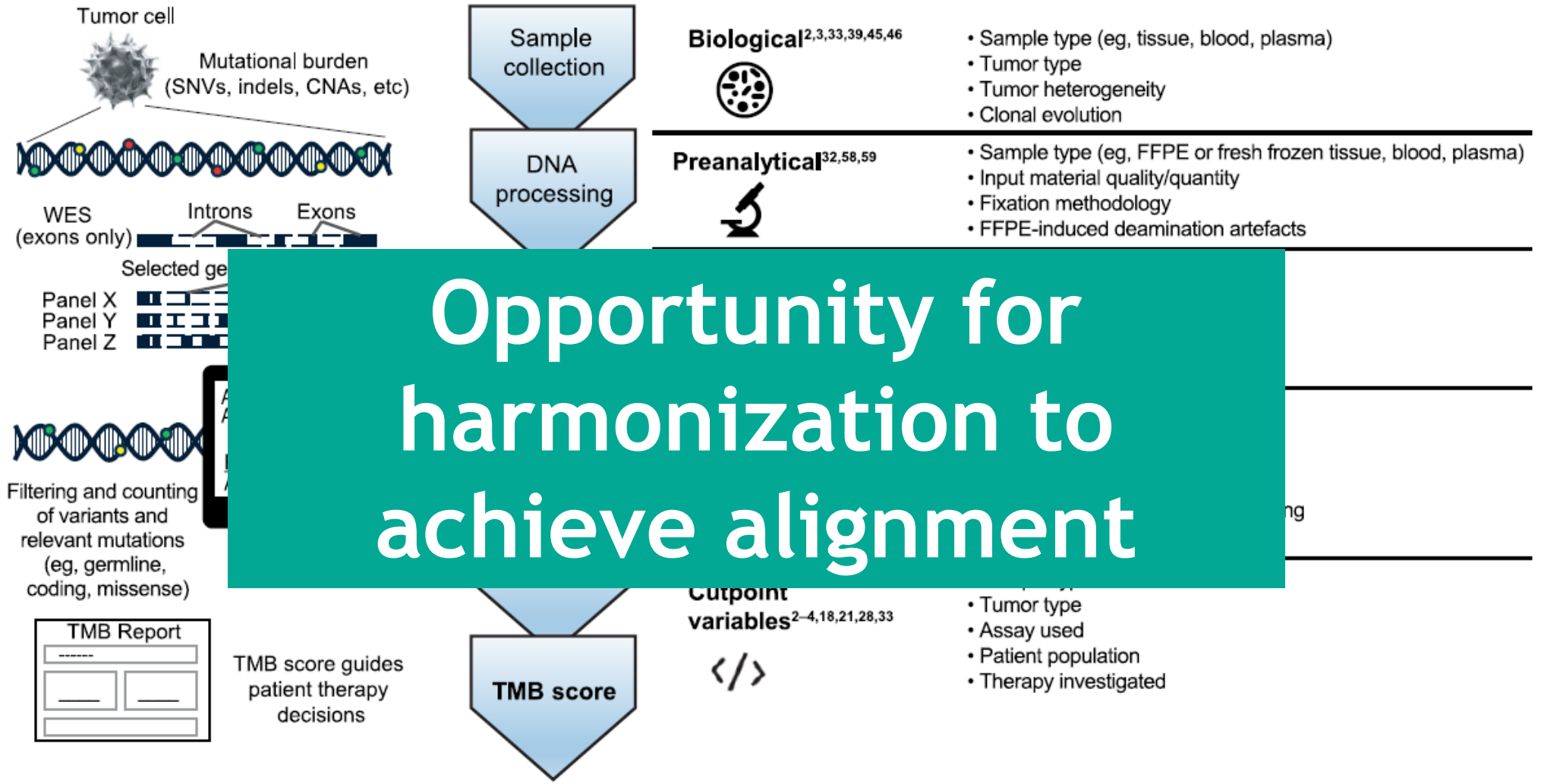
Factors That Impact TMB Estimation

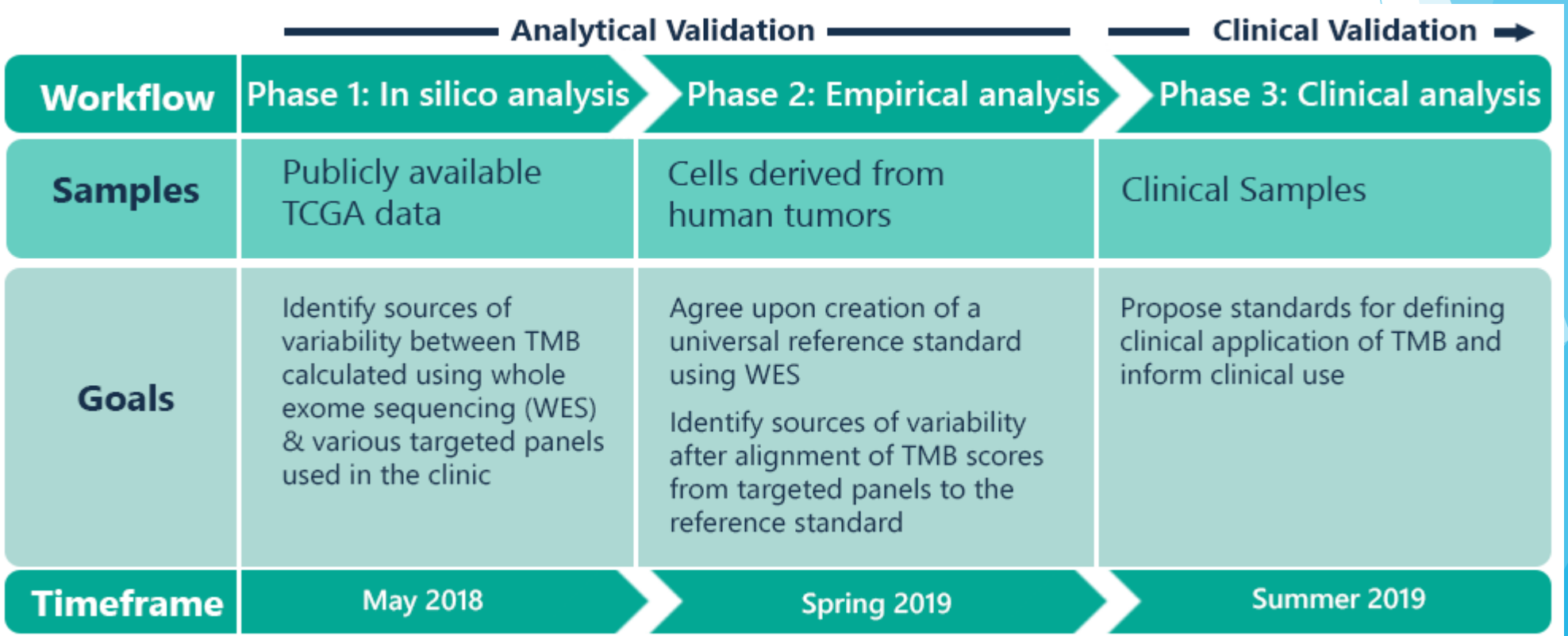


Opportunity for harmonization to achieve alignment

Stenzinger A, Allen JD, et al. *Genes Chromosomes Cancer*. 2019.

Friends of Cancer Research TMB Harmonization Effort

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



www.focr.org/tmb

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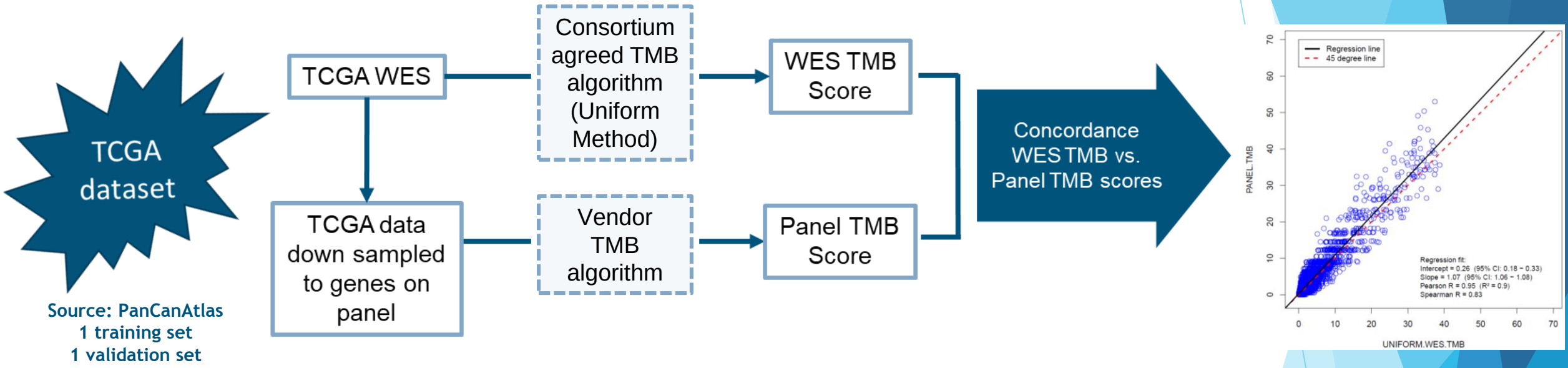
Phase 1: In silico analysis



Multi-stakeholder team: **ACT Genomics, AstraZeneca**, Bristol-Myers Squibb, **Caris Life Sciences**, Columbia University, EMD Serono, **Foundation Medicine**, Genentech, **Guardant Health, Illumina**, Johns Hopkins University, **Memorial Sloan Kettering Cancer Center**, Merck, National Cancer Institute, **NeoGenomics Laboratories**, OmniSeq, Pfizer, **Personal Genome Diagnostics**, precisionFDA, **QIAGEN**, Regeneron Pharmaceuticals, SeraCare, **Thermo Fisher Scientific**, U.S. FDA

***bolded** = panel examined in the in silico analysis

Phase 1 Conclusions

- Panel-TMB was strongly correlated to WES-TMB in TCGA samples
- Associations between panel-TMB and WES-TMB were observed to differ by cancer type
- Theoretical variation in TMB quantification across panel-based diagnostic platforms exists and warrants empirical alignment with reference standard

Recommendations:

- Common definition of TMB to ensure reporting consistency
- Standardization of analytical validation studies
- Alignment against external reference standard

Phase 2A: Empirical analysis- Cell Lines

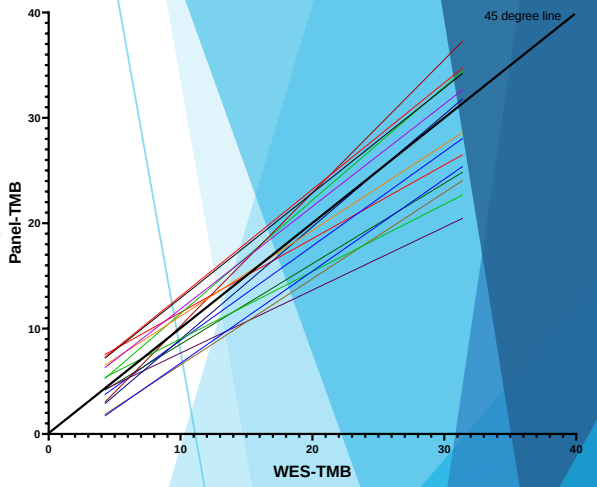
Cell Lines

10 tumor-normal matched
Human cell lines (ATCC)
Breast and lung cancer

Cell line WES → Consortium agreed TMB algorithm → External Reference Standard

Cell line NGS Panel → Vendor TMB algorithm → Panel TMB Score

Reference standard alignment using panel TMB vs. WES



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***bolded** = panel examined in the empirical analysis

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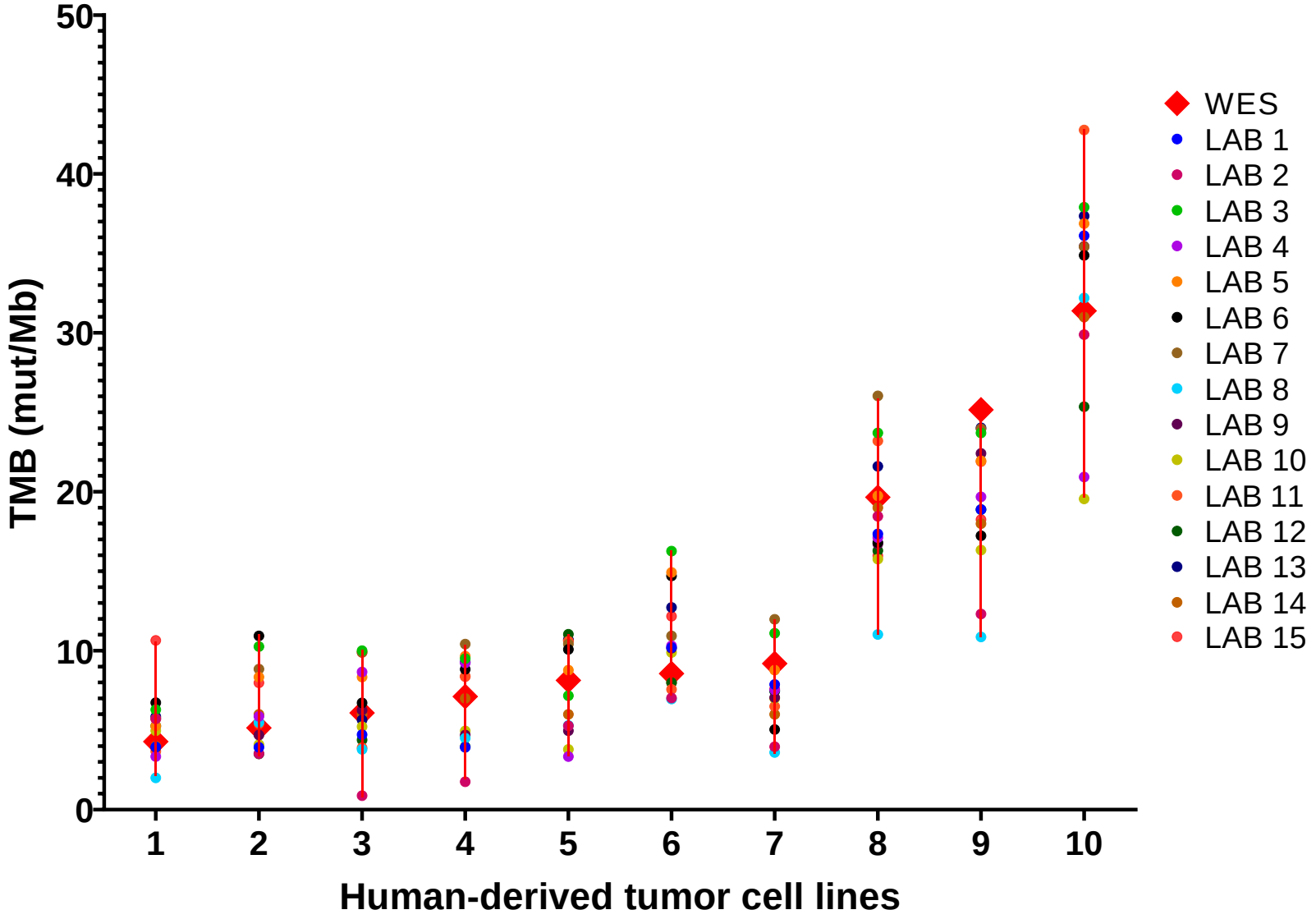
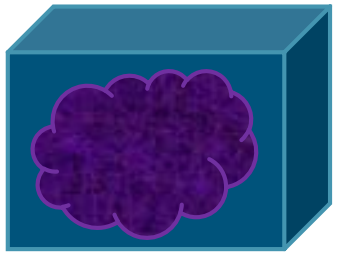
Variability in TMB estimates for each tumor cell line across all 15 participating laboratories



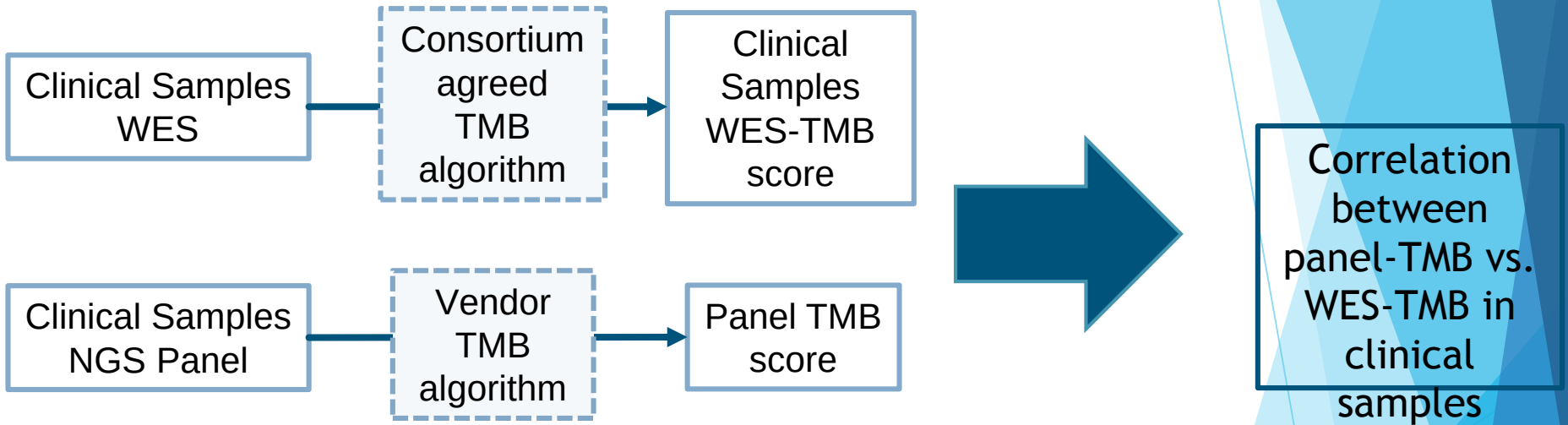
Phase 2B: Empirical analysis- Clinical Samples

Clinical Samples



30 tumor-normal matched FFPE clinical samples (CHTN)

Five different cancer types



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***bolded** = panel examined in the empirical analysis

Multistakeholder International Collaboration

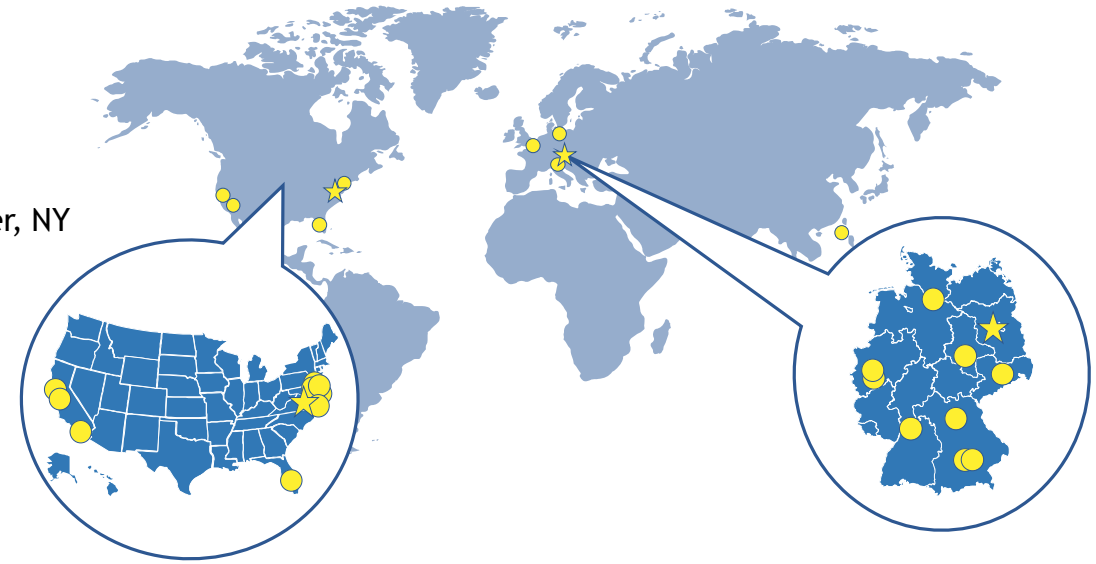
Partners:

Diagnostic
- ACT Genomics Company, Ltd
- Caris Life Sciences, Inc
- Foundation Medicine, Inc
- Guardant Health, Inc
- Illumina, Inc
- Navican
- NeoGenomics Laboratories, Inc
- OmniSeq, Inc
- Personal Genome Diagnostics, Inc
- Q^2 | EA Genomics
- QIAGEN, NV
- Thermo Fisher Scientific, Inc

Academic
- Brigham & Women's Hospital, MA
- Columbia University, NY
- Memorial Sloan Kettering Cancer Center, NY
- Johns Hopkins University, MD

Pharmaceutical
- AstraZeneca, LP
- Bristol-Myers Squibb Company, Inc
- EMD Serono, Inc
- Genentech, Inc
- Merck & Company, Inc
- Pfizer, Inc
- Regeneron Pharmaceuticals, Inc

Other
- EORTC
- NIH National Cancer Institute
- precisionFDA
- SeraCare Life Sciences, Inc
- US Food and Drug Administration



QuiP
Quality in Pathology

Partners:

Diagnostic
- Foundation Medicine, Inc
- Illumina, Inc
- NEO New Oncology, AG
- QIAGEN, NV
- Thermo Fisher Scientific, Inc

Academic
- Charité Berlin
- LMU Munich
- Technical University Munich
- University Hospital Cologne
- University Hospital Dresden
- University Hospital Erlangen
- University Hospital Halle (Saale)
- University Hospital Heidelberg
- University Hospital Regensburg
- University Hospital Zurich

Pharmaceutical
- Bristol-Myers Squibb Company, Inc
- Merck Sharp & Dohme, Ltd
- F. Hoffmann-La Roche, AG

Other
- German Cancer Consortium (DKTK)
- Institute for Hematopathology, Hamburg

Stenzinger A, Allen JD, et al. *Genes Chromosomes Cancer*.

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Policy Opportunities Beyond TMB

- Demonstrate opportunities for the use of *in silico* and human-derived cell line reference material to optimize diagnostic development
- Inform policy discussions on optimal trial strategies for quantitative biomarkers, diagnostic and drug labeling considerations, and regulatory pathways
- Consortium effort as a model for future harmonization efforts

FRIENDS of CANCER RESEARCH

TMB Harmonization Consortium

- ACT Genomics
- AstraZeneca
- Brigham & Women's Hospital
- Bristol-Myers Squibb
- Caris Life Sciences
- Columbia University
- EMD Serono
- European Organisation for Research and Treatment of Cancer (EORTC)
- Foundation Medicine
- Guardant Health
- Illumina
- Johns Hopkins University
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- National Institutes of Health (NIH)
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