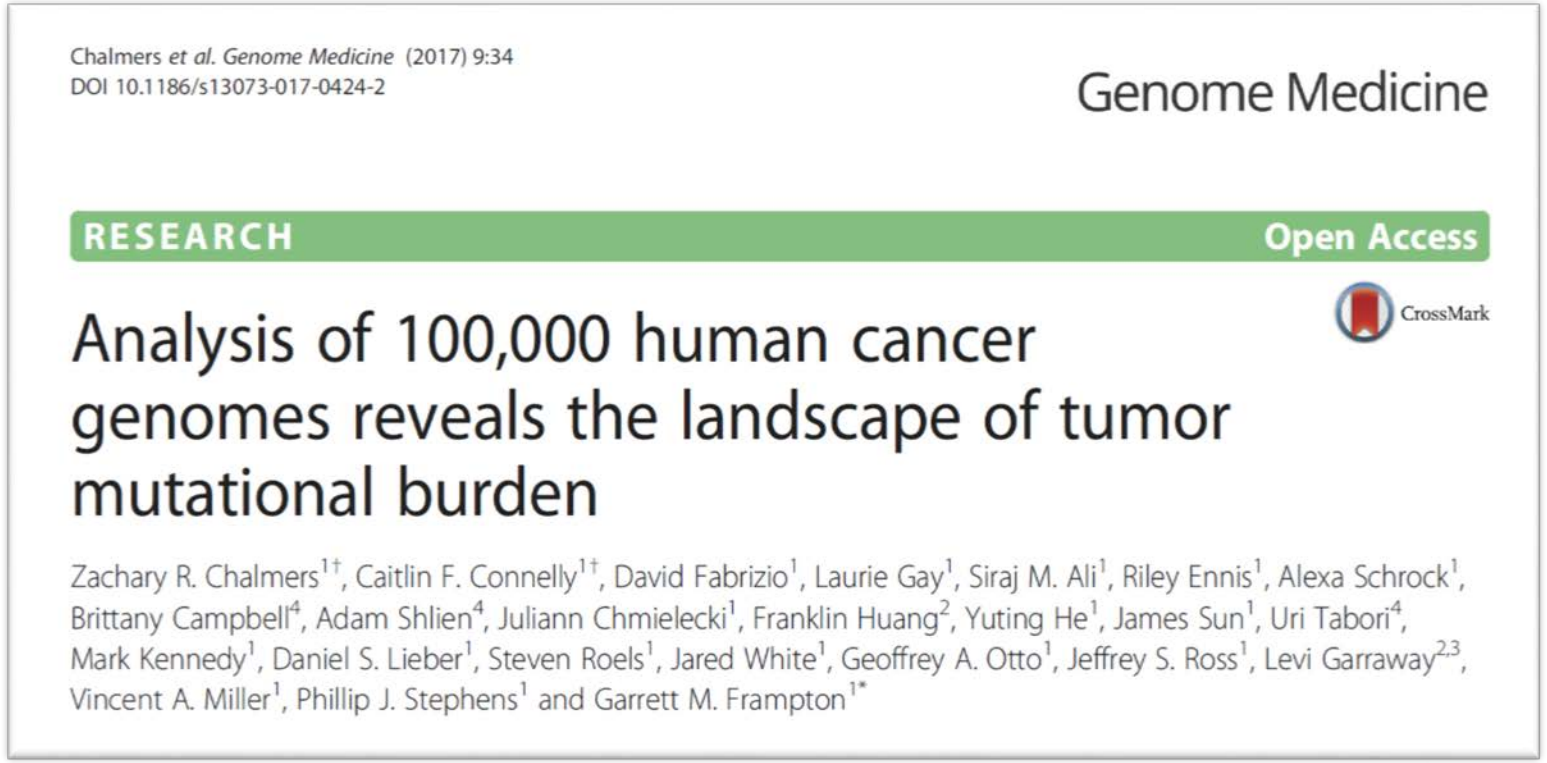

Chalmers *et al. Genome Medicine* (2017) 9:34
DOI 10.1186/s13073-017-0424-2

Genome Medicine

RESEARCH Open Access

Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

Zachary R. Chalmers[1†], Caitlin F. Connelly[1†], David Fabrizio[1], Laurie Gay[1], Siraj M. Ali[1], Riley Ennis[1], Alexa Schrock[1], Brittany Campbell[4], Adam Shlien[4], Juliann Chmielecki[1], Franklin Huang[2], Yuting He[1], James Sun[1], Uri Tabori[4], Mark Kennedy[1], Daniel S. Lieber[1], Steven Roels[1], Jared White[1], Geoffrey A. Otto[1], Jeffrey S. Ross[1], Levi Garraway[2,3], Vincent A. Miller[1], Phillip J. Stephens[1] and Garrett M. Frampton[1*]

2017/04 Published

TMB Paper Review

2018/05/08

Kijin Kim

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Cancer Immunotherapy

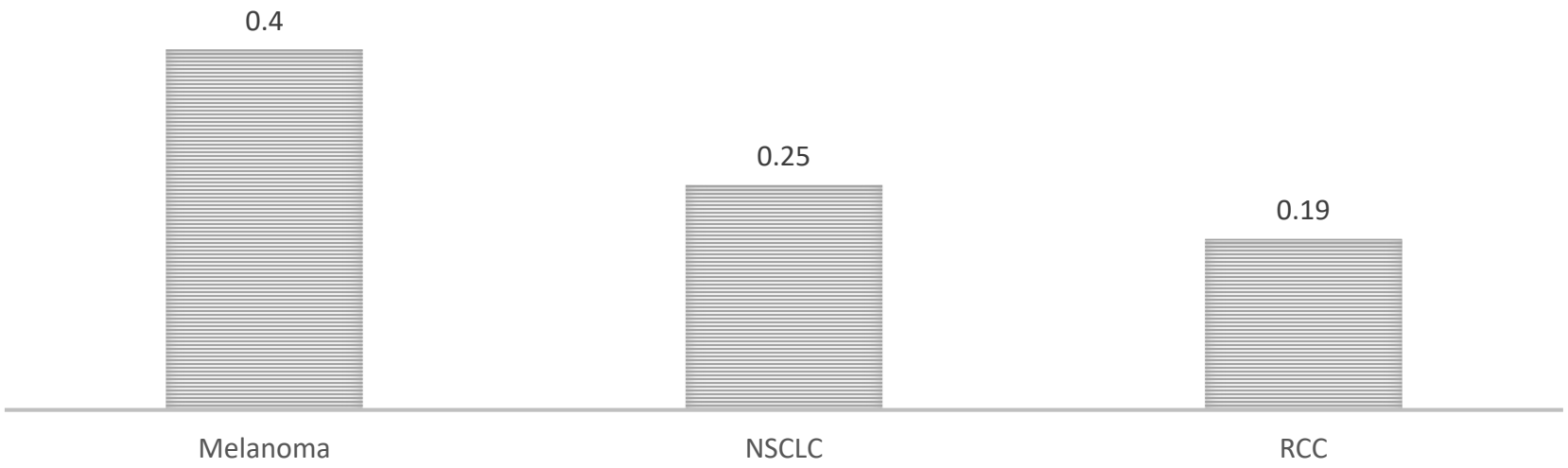
Helping Predict Response with Tumor Mutational Burden

Cancer immunotherapies have the potential to treat cancer by harnessing the power of our own immune systems. But right now, only about 20-40% of people respond to this important class of therapy.[1,2] Learn about a quantitative clinical biomarker, tumor mutational burden (TMB), that can help identify patients who may be more likely to benefit from cancer immunotherapies.[3]

LEARN MORE ABOUT TMB →

Immune Checkpoint Blockade Immunotherapy

RESPONSE RATES TO SINGLE-AGENT PD-1/PD-L1 INHIBITION



Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers, Aaron M. Goodman, et al. (2017)

TMB (Tumor Mutational Burden)

= Measurement of somatic mutations within a tumor

Companion Diagnostic, Pharmacogenomic, and Cancer Biomarkers

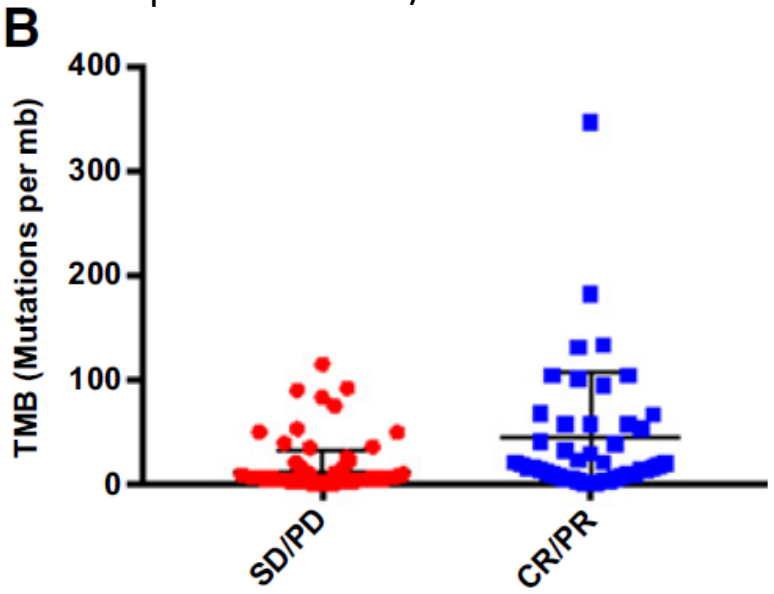
Molecular Cancer Therapeutics

Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers

Aaron M. Goodman[1,2,3], Shumei Kato[1,2], Lyudmila Bazhenova[1], Sandip P. Patel[1], Garrett M. Frampton[4], Vincent Miller[4], Philip J. Stephens[4], Gregory A. Daniels[1], and Razelle Kurzrock[1,2]

2017/11 Published

Responses to PD-1/PD-L1 immunotherapy



SD, stable disease; PD, progressive disease; CR, complete response; PR, partial response

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Genome Medicine

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Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden

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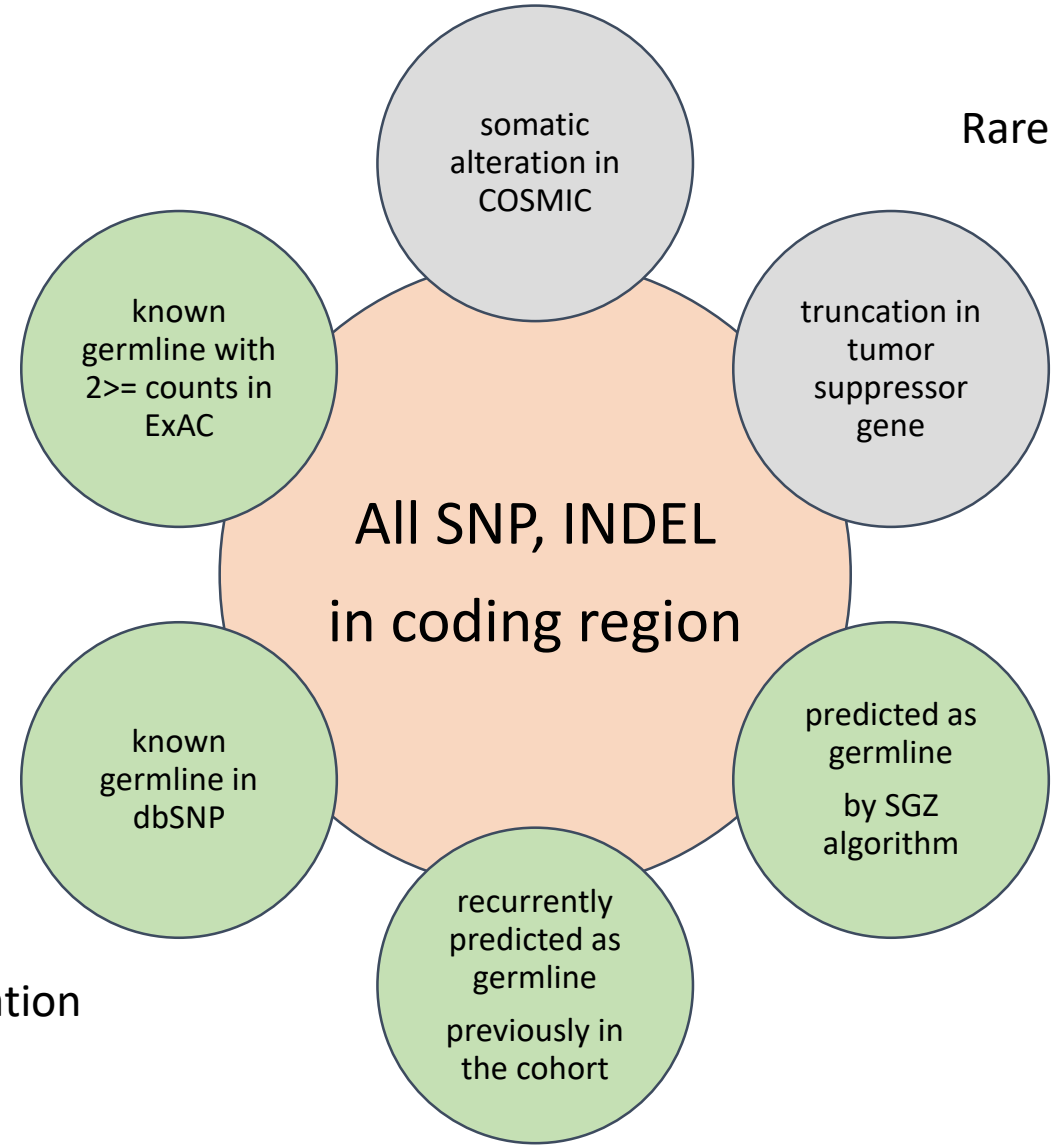
Objective

- TMB in WES → TMB in Smaller gene set
- Understanding landscape of TMB based on > 100,000 CGP data
- Identifying association between certain gene mutation and TMB

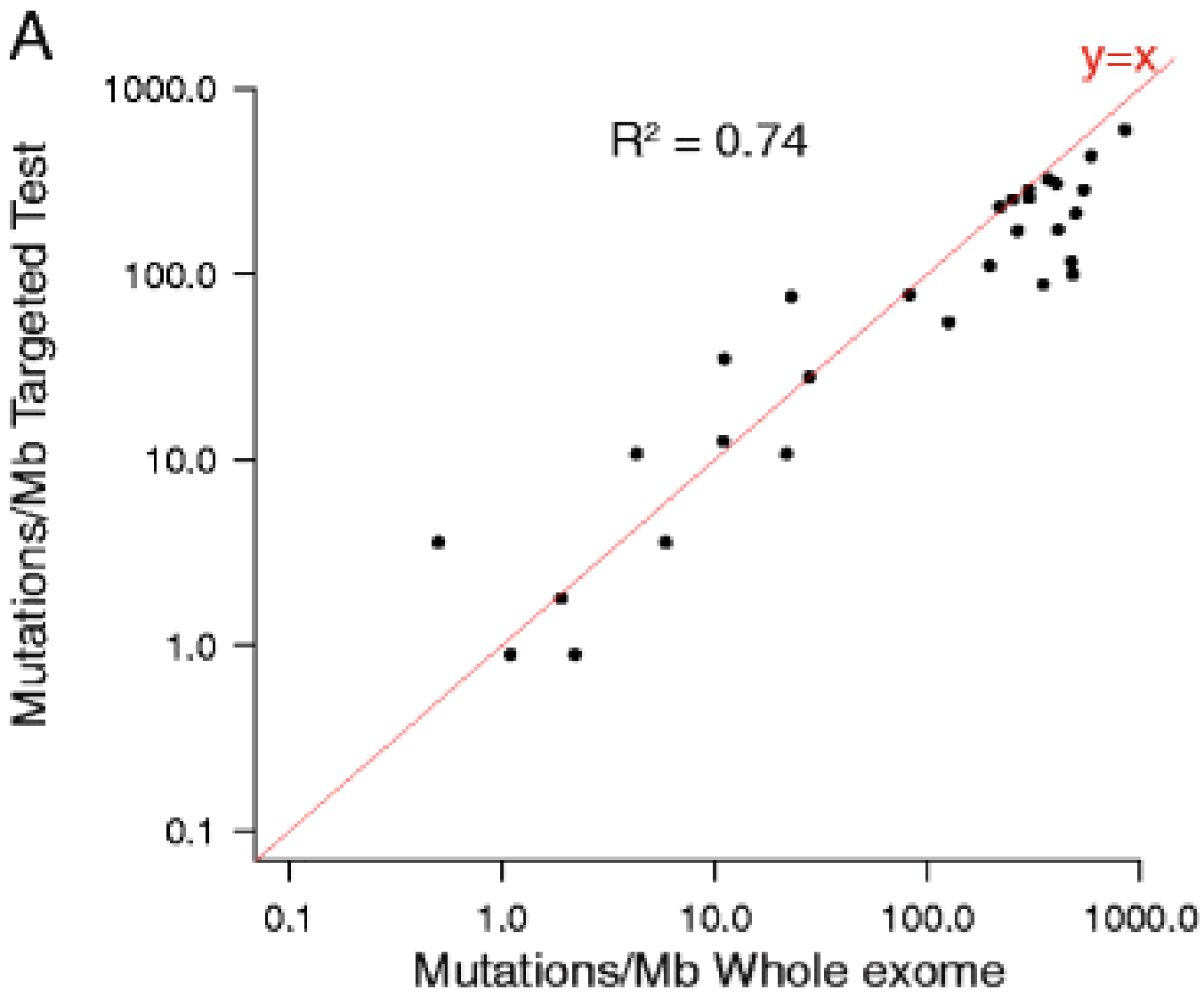
Define TMB



$$\text{TMB} = \frac{\text{\# of mutations}}{\text{Size of coding region (Mb)}}$$

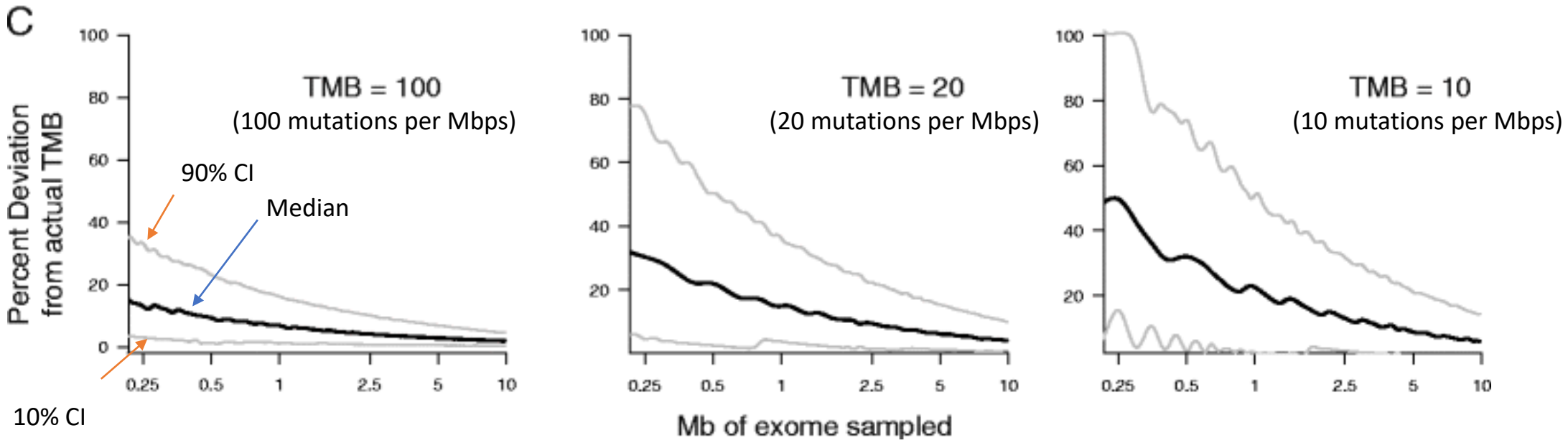
WES vs CGP in TMB analysis

- 29 samples sequenced both on exome and gene panel (CGP)
- Gene panel targets 315 genes (1.1 Mb of coding genome) using FoundationOne CDx™
- WES sequence both tumor and normal, CGP only tumor


A
y=x
R² = 0.74
1000.0
100.0
10.0
1.0
0.1
Mutations/Mb Targeted Test
0.1
1.0
10.0
100.0
1000.0
Mutations/Mb Whole exome

Downsampling simulation

$$\text{Percent deviation (\%)} = \frac{\text{simulated} - \text{expected}}{\text{expected}} \times 100$$



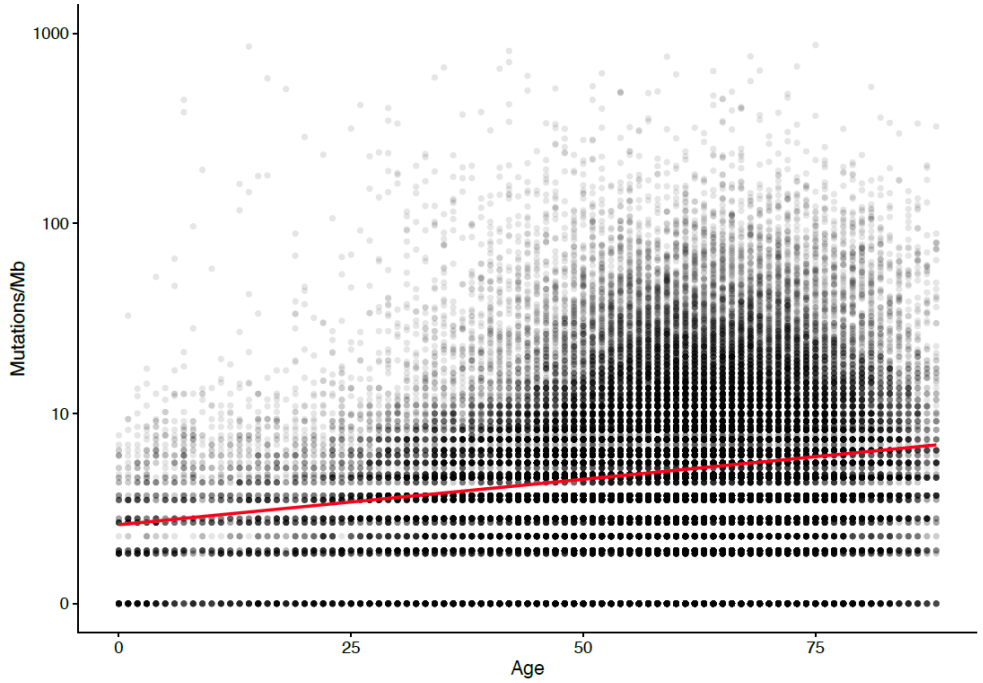
Sampling 1000 times for each TMB (binomial distribution) and sequencing amounts

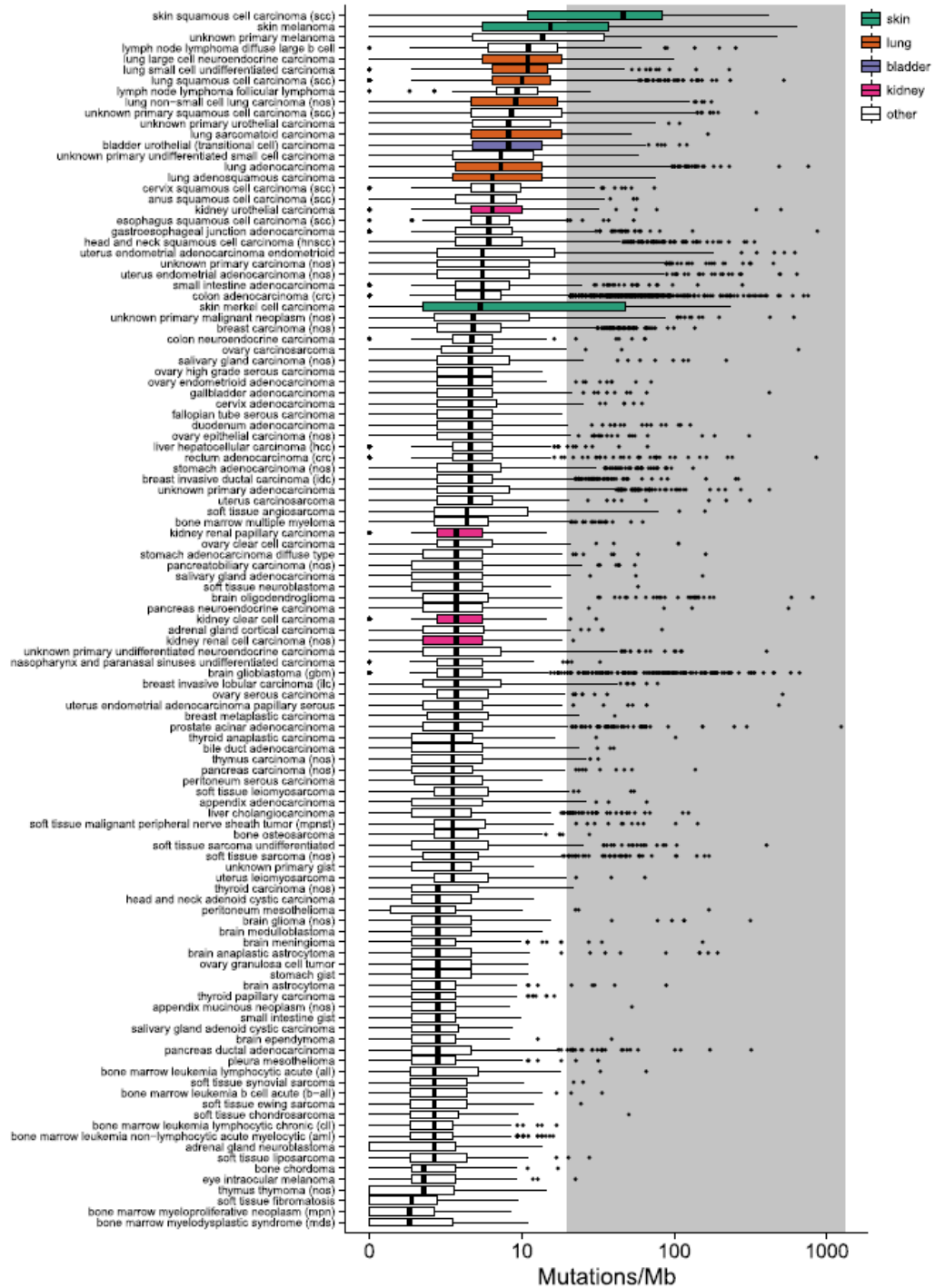
TCGA data analysis

- WES profiles from 8917 cancer specimens
- Calculate TMB from 315 gene set (1.1 Mb of coding genome)
- Highly correlated (R^2 = 0.98)

CGP TMB analysis

- Used FoundationOne CDx™
- Used 92,439 samples (only tumor) which has >300x exon coverage
- 541 distinct cancer types
- Median : 3.6 mutations/Mb
- TMB increase with aging



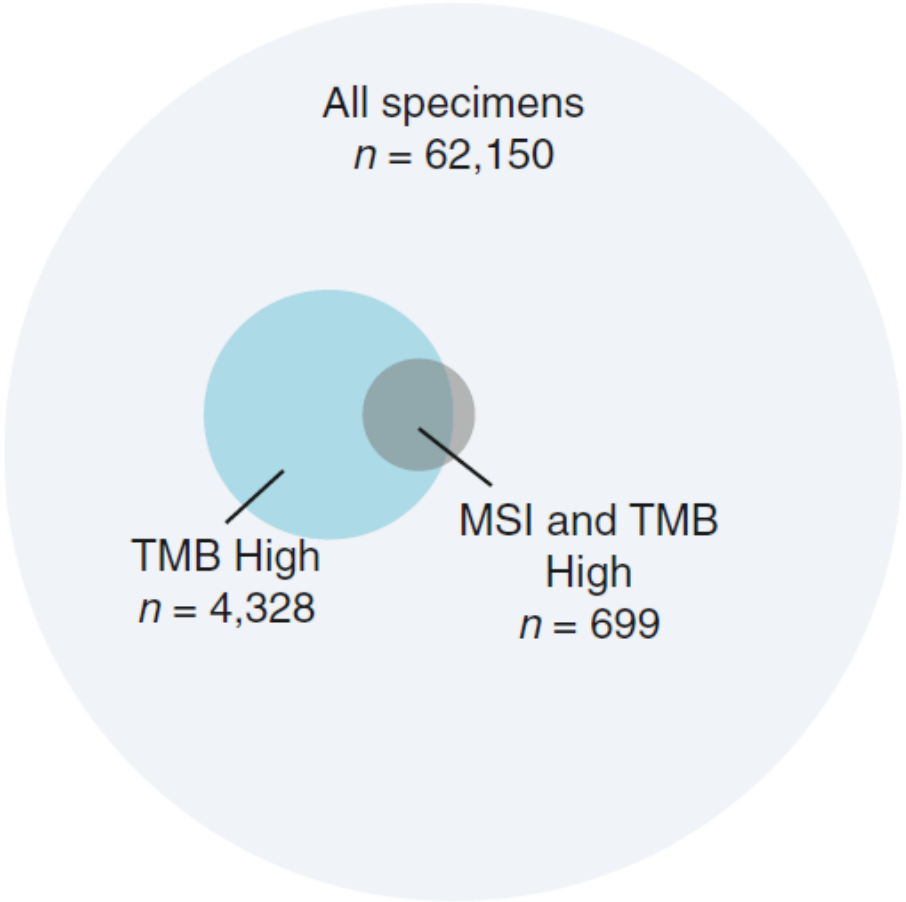

skin squamous cell carcinoma (scc)
skin melanoma
unknown primary melanoma
lymph node lymphoma diffuse large b cell
lung large cell neuroendocrine carcinoma
lung small cell undifferentiated carcinoma
lung squamous cell carcinoma (scc)
lymph node lymphoma follicular lymphoma
lung non-small cell lung carcinoma (nos)
unknown primary squamous cell carcinoma (scc)
unknown primary urothelial carcinoma
lung sarcomatoid carcinoma
bladder urothelial (transitional cell) carcinoma
unknown primary undifferentiated small cell carcinoma
lung adenocarcinoma
lung adenosquamous carcinoma
cervix squamous cell carcinoma (scc)
anus squamous cell carcinoma (scc)
kidney urothelial carcinoma
esophagus squamous cell carcinoma (scc)
gastroesophageal junction adenocarcinoma
head and neck squamous cell carcinoma (hnscc)
uterus endometrial adenocarcinoma endometrioid
unknown primary carcinoma (nos)
uterus endometrial adenocarcinoma (nos)
small intestine adenocarcinoma
colon adenocarcinoma (crc)
skin merkel cell carcinoma
unknown primary malignant neoplasm (nos)
breast carcinoma (nos)
colon neuroendocrine carcinoma
ovary carcinosarcoma
salivary gland carcinoma (nos)
ovary high grade serous carcinoma
ovary endometrioid adenocarcinoma
gallbladder adenocarcinoma
cervix adenocarcinoma
fallopian tube serous carcinoma
duodenum adenocarcinoma
ovary epithelial carcinoma (nos)
liver hepatocellular carcinoma (hcc)
rectum adenocarcinoma (crc)
stomach adenocarcinoma (nos)
breast invasive ductal carcinoma (idc)
unknown primary adenocarcinoma
uterus carcinosarcoma
soft tissue angiosarcoma
bone marrow multiple myeloma
kidney renal papillary carcinoma
ovary clear cell carcinoma
stomach adenocarcinoma diffuse type
pancreatobiliary carcinoma (nos)
salivary gland adenocarcinoma
soft tissue neuroblastoma
brain oligodendroglioma
pancreas neuroendocrine carcinoma
kidney clear cell carcinoma
adrenal gland cortical carcinoma
kidney renal cell carcinoma (nos)
unknown primary undifferentiated neuroendocrine carcinoma
nasopharynx and paranasal sinuses undifferentiated carcinoma
brain glioblastoma (gbm)
breast invasive lobular carcinoma (ilc)
ovary serous carcinoma
uterus endometrial adenocarcinoma papillary serous
breast metaplastic carcinoma
prostate acinar adenocarcinoma
thyroid anaplastic carcinoma
bile duct adenocarcinoma
thymus carcinoma (nos)
pancreas carcinoma (nos)
peritoneum serous carcinoma
soft tissue leiomyosarcoma
appendix adenocarcinoma
liver cholangiocarcinoma
soft tissue malignant peripheral nerve sheath tumor (mpnst)
bone osteosarcoma
soft tissue sarcoma undifferentiated
soft tissue sarcoma (nos)
unknown primary gist
uterus leiomyosarcoma
thyroid carcinoma (nos)
head and neck adenoid cystic carcinoma
peritoneum mesothelioma
brain glioma (nos)
brain medulloblastoma
brain meningioma
brain anaplastic astrocytoma
ovary granulosa cell tumor
stomach gist
brain astrocytoma
thyroid papillary carcinoma
appendix mucinous neoplasm (nos)
small intestine gist
salivary gland adenoid cystic carcinoma
brain ependymoma
pancreas ductal adenocarcinoma
pleura mesothelioma
bone marrow leukemia lymphocytic acute (all)
soft tissue synovial sarcoma
bone marrow leukemia b cell acute (b-all)
soft tissue ewing sarcoma
soft tissue chondrosarcoma
bone marrow leukemia lymphocytic chronic (cll)
bone marrow leukemia non-lymphocytic acute myelocytic (aml)
adrenal gland neuroblastoma
soft tissue liposarcoma
bone chordoma
eye intraocular melanoma
thymus thymoma (nos)
soft tissue fibromatosis
bone marrow myeloproliferative neoplasm (mpn)
bone marrow myelodysplastic syndrome (mds)
skin
lung
bladder
kidney
other
0
10
100
1000
Mutations/Mb

Disease indications with greater than 5% of specimens showing high TMB (>20 mutations/Mb)

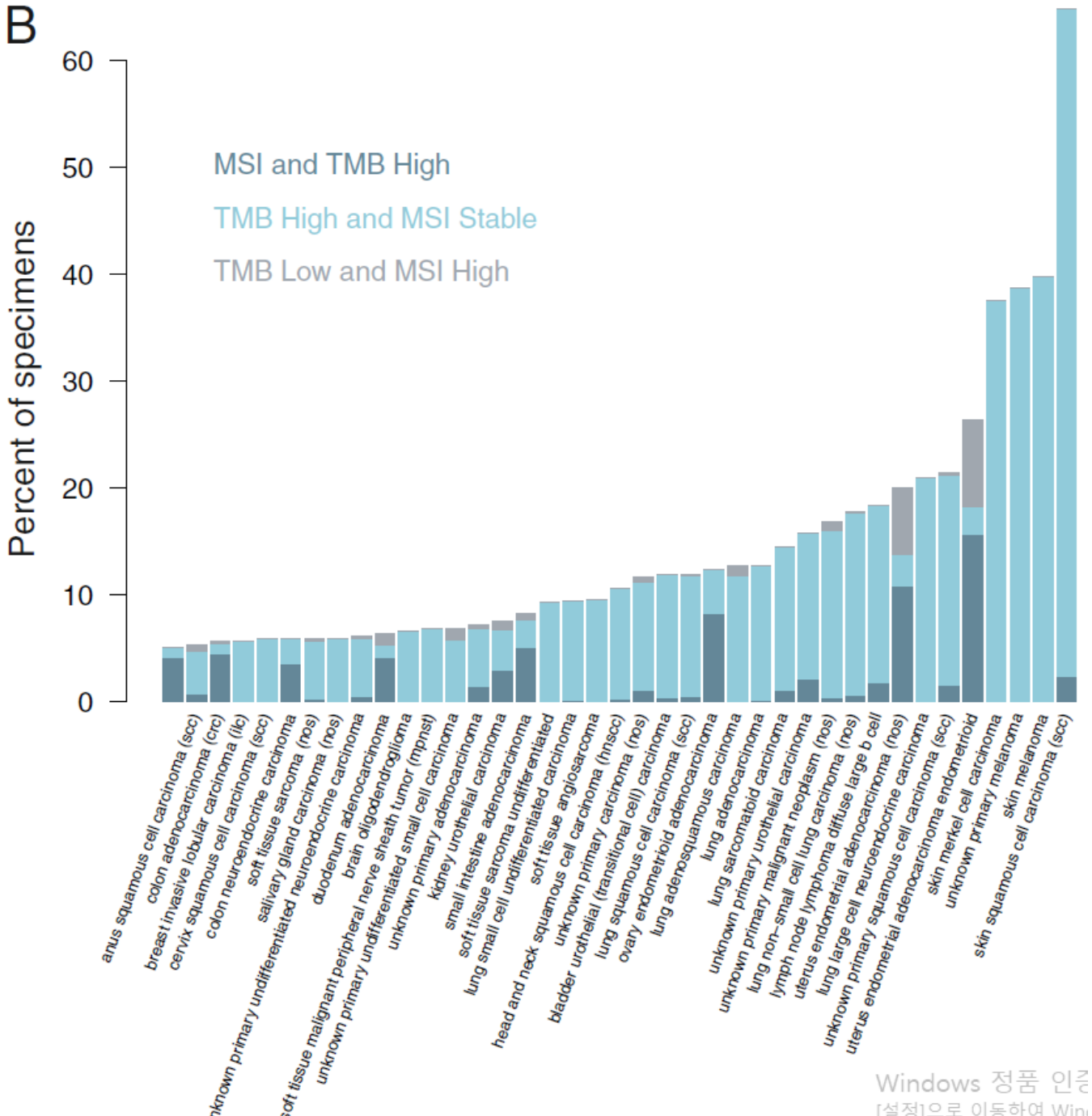
Disease type	Specimen count	Median TMB
skin basal cell carcinoma	92	47.3
skin squamous cell carcinoma (scc)	266	45.2
skin melanoma	879	14.4
unknown primary melanoma	1324	12.6
lung large cell carcinoma	74	12.2
lymph node lymphoma diffuse large b cell	348	10.0
lung large cell neuroendocrine carcinoma	288	9.9
lung small cell undifferentiated carcinoma	913	9.9
lung squamous cell carcinoma (scc)	2102	9.0
lung non-small cell lung carcinoma (nos)	2636	8.1
bladder carcinoma (nos)	77	8.1
unknown primary squamous cell carcinoma (scc)	606	7.6
lung sarcomatoid carcinoma	130	7.2
unknown primary urothelial carcinoma	188	7.2
bladder urothelial (transitional cell) carcinoma	1218	7.2
head and neck melanoma	59	6.3
lung adenocarcinoma	11855	6.3
lymph node lymphoma b-cell (nos)	88	6.3
unknown primary undifferentiated small cell carcinoma	117	6.3

TMB and MSI

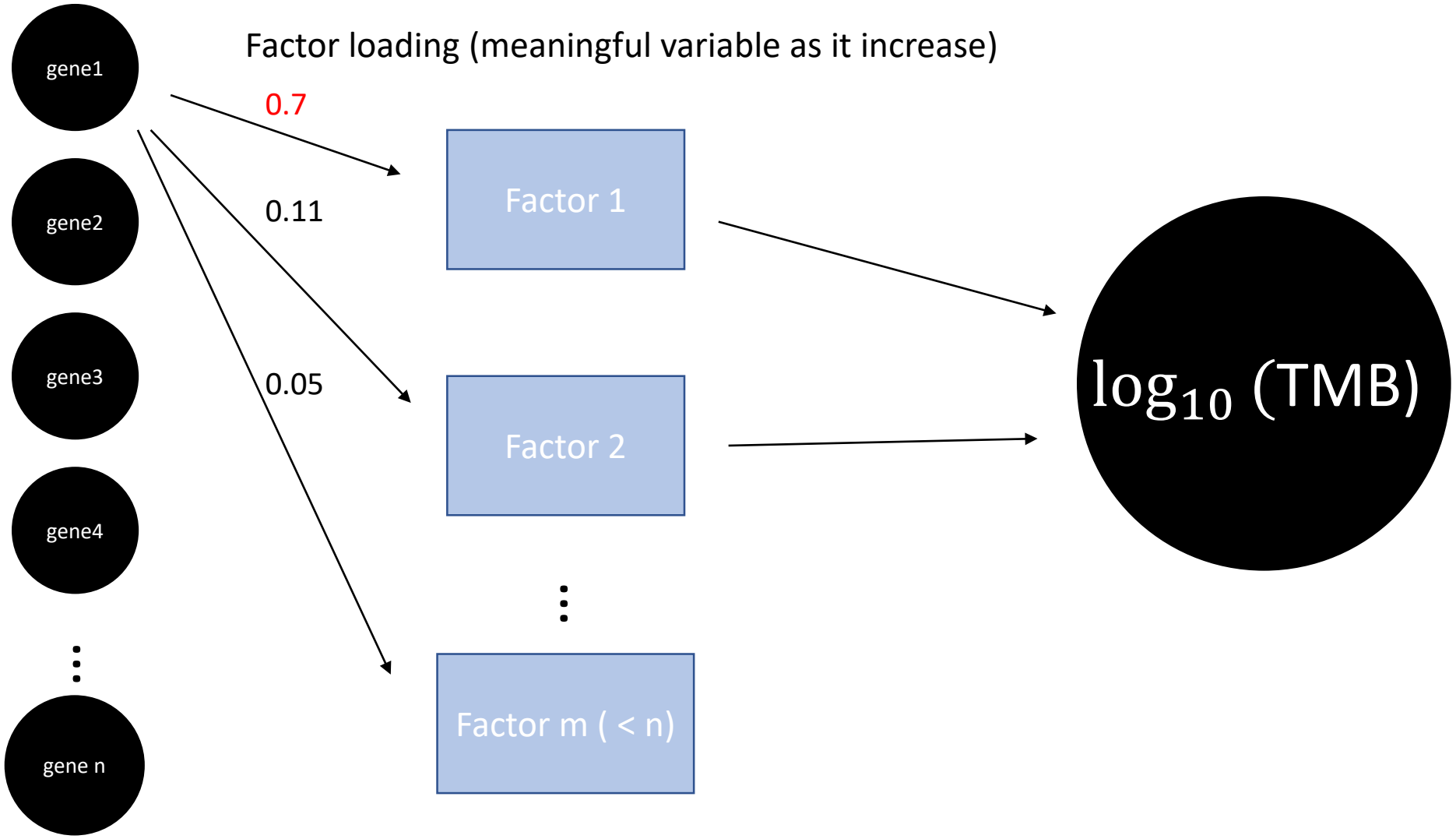
A

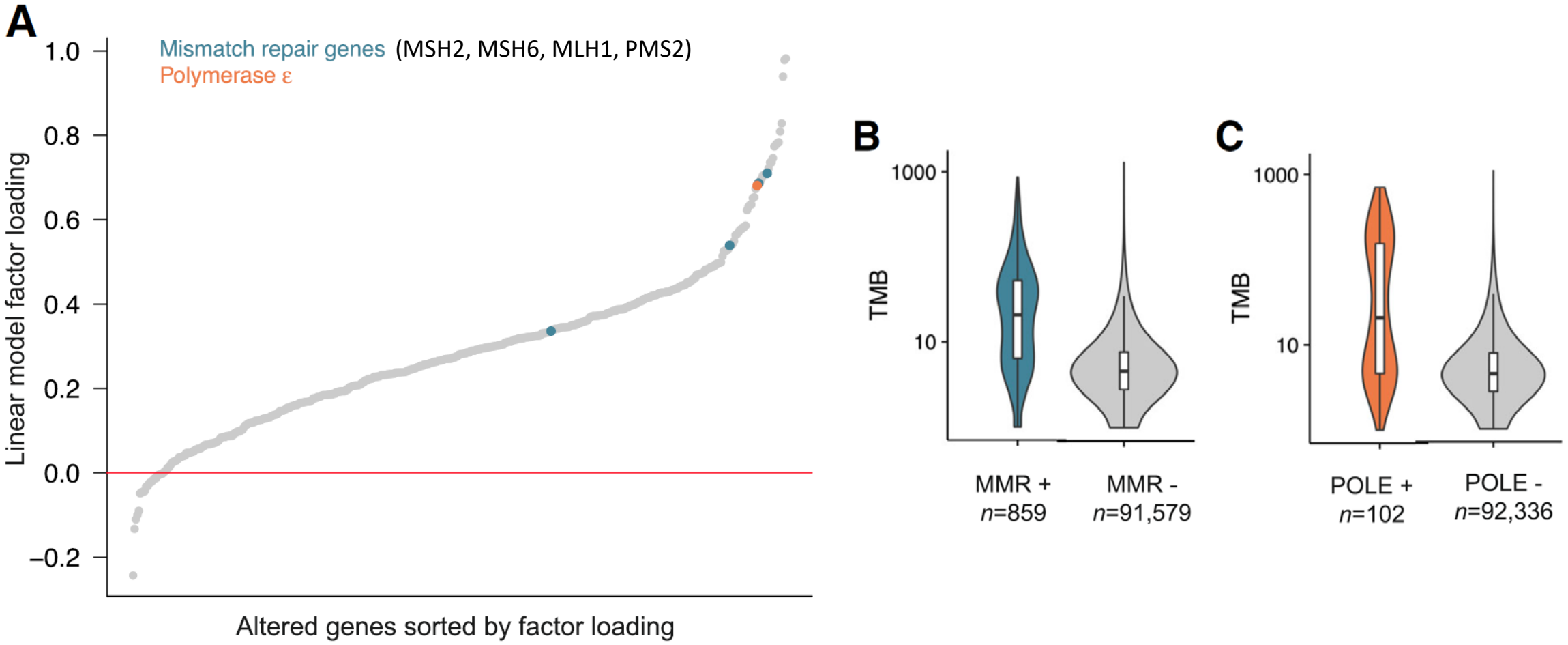


B

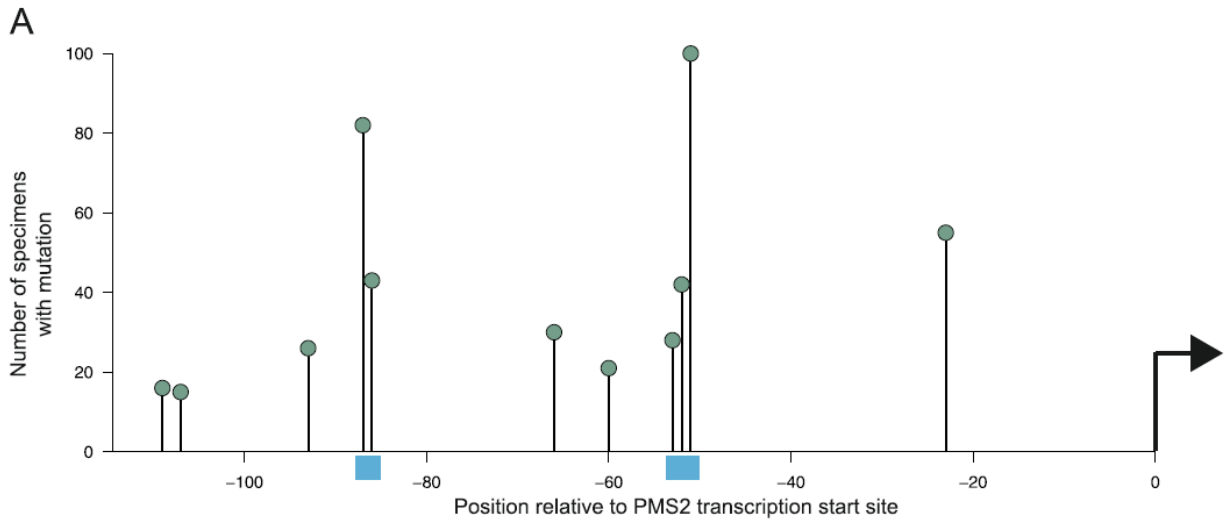


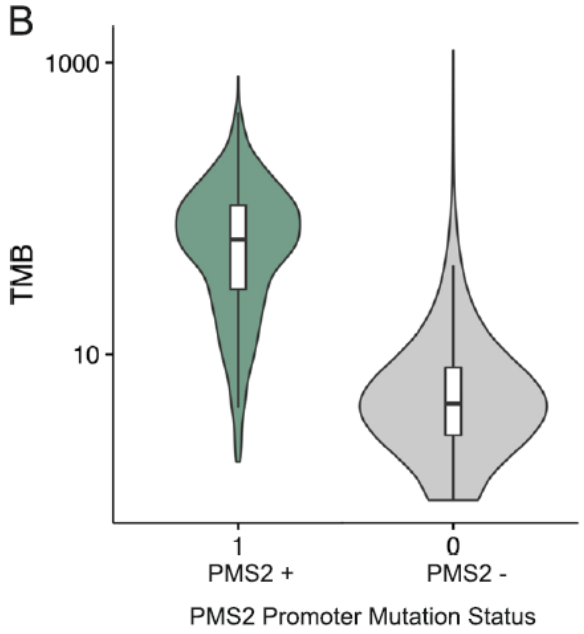
TMB increase-associated genes and mutations




A
Mismatch repair genes (MSH2, MSH6, MLH1, PMS2)
Polymerase ε
Linear model factor loading
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
Altered genes sorted by factor loading
B
TMB
1000
10
MMR +
n=859
MMR -
n=91,579
C
TMB
1000
10
POLE +
n=102
POLE -
n=92,336

PMS2 promoter region mutation





Discussion

- 1.1Mb CGP assay agree well with WES TMB
- Filtering out germline alteration and rare variants is important to obtaining accurate measurement of TMB
- Sampling variation increase as sequenced size (Mb) decrease, especially at lower levels of TMB
- Extensive landscape of TMB across hundreds of genes including newly found TMB associated region, PMS2 promoter