

How Can Genomics Guide Decision-Making in the Application of Immunotherapy?

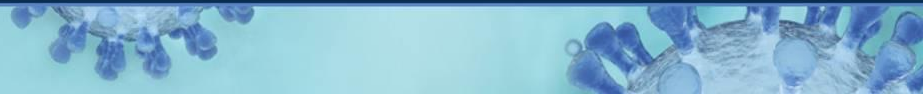
Colin C. Pritchard MD, PhD

University of Washington, Dept. of Lab Medicine

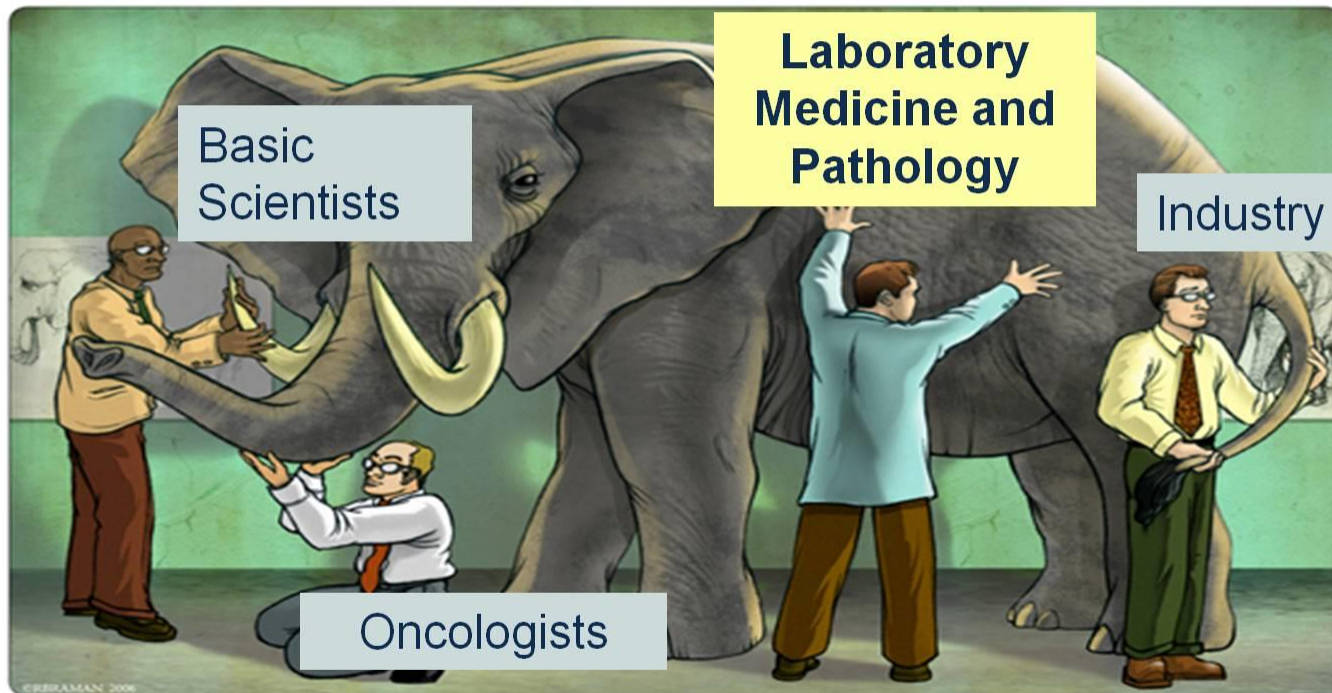
Jan. 26, 2018 ASCO-SITC

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Immunotherapy



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Presented By Colin Pritchard at 2018 ASCO-SITC Clinical Immuno-Oncology Symposium

May 23, 2017



The screenshot shows the FDA website header with the logo and navigation menu. The main content area displays a news release titled "FDA approves first cancer treatment for any solid tumor with a specific genetic feature". Below the title are social media sharing buttons for Facebook, Twitter, LinkedIn, Pinterest, Email, and Print.

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FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

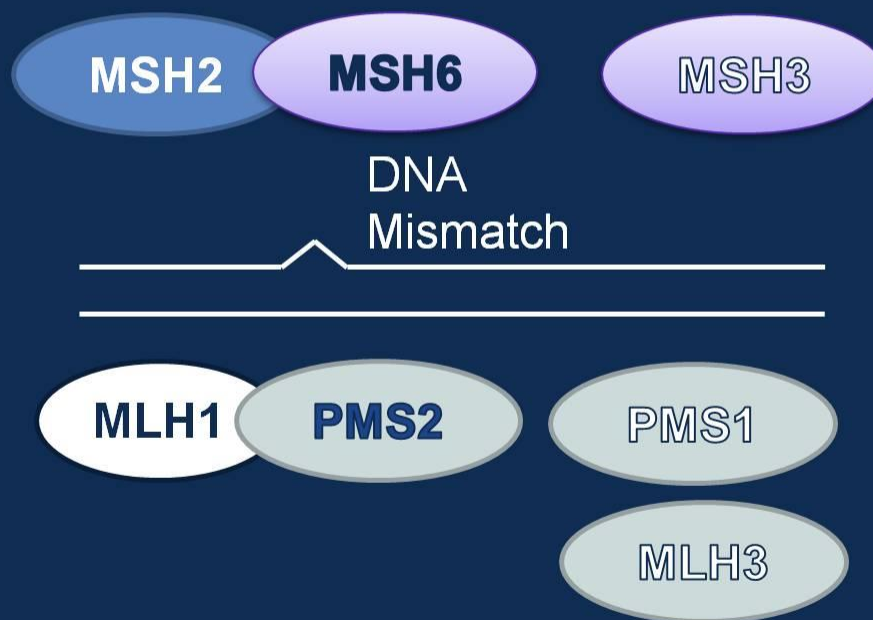
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Mismatch DNA Repair (MMR)

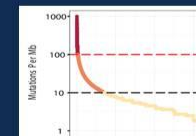
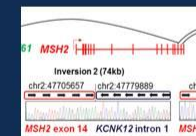
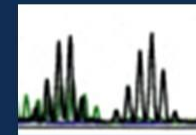


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MMR Deficiency Detection Methods

- Immunohistochemistry (protein expression)
- MSI by PCR capillary electrophoresis
- MSI by NGS
- MMR gene tumor sequencing
- Total mutation burden (not specific to MMR)

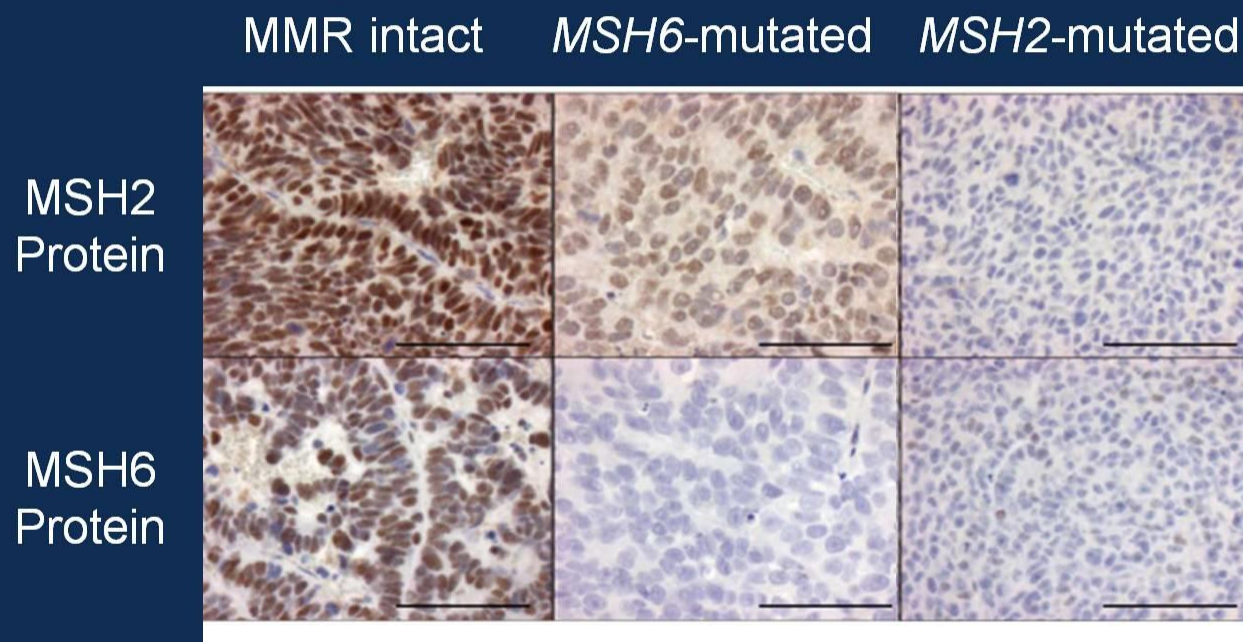


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Mismatch Repair By IHC



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What is Microsatellite Instability?

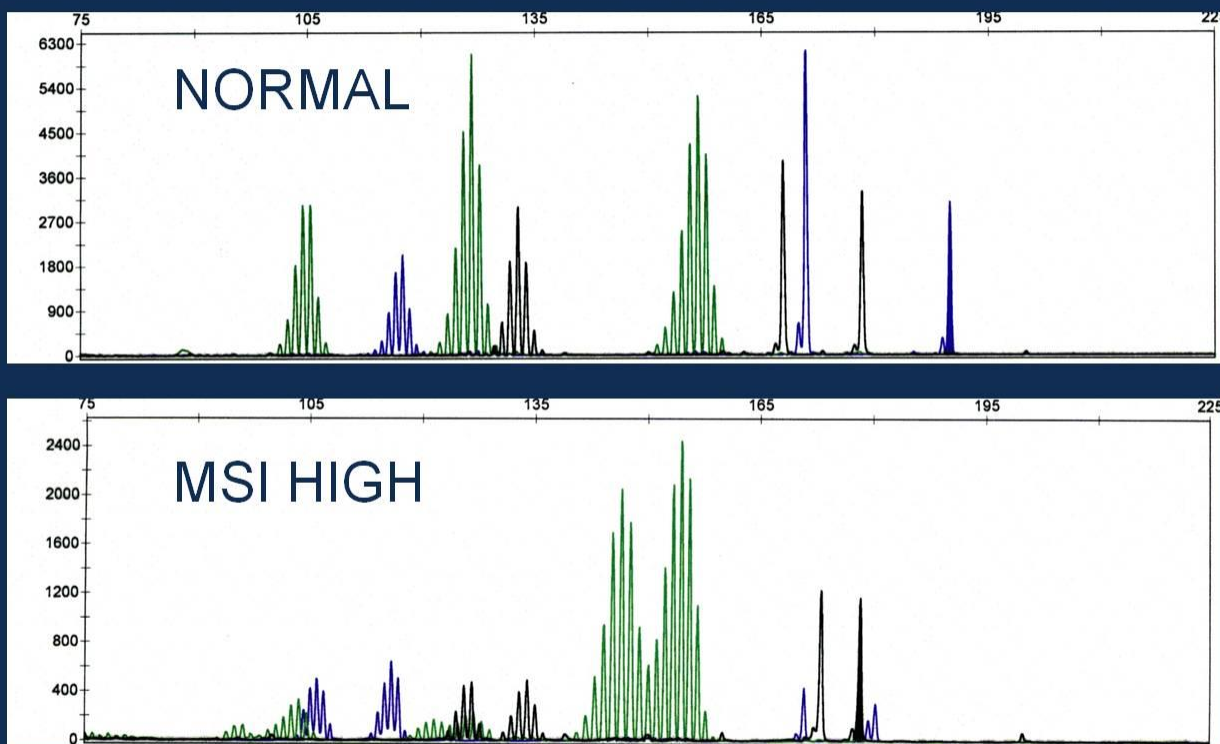
- Caused by loss of mismatch repair function
- Short repetitive tracks of DNA (microsatellites) are mutated throughout genome
- Typically inferred from only 5 loci selected for optimal performance in colorectal cancer

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MSI by PCR (Promega 5-marker)

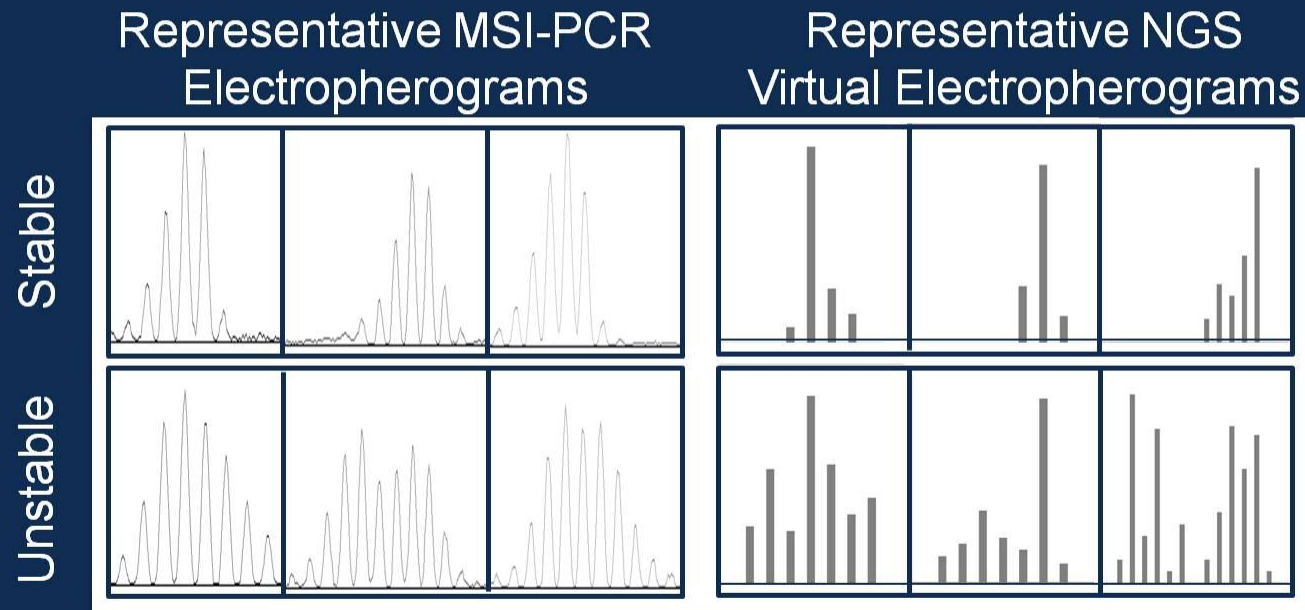


Source: UW Genetics and Solid Tumors Lab

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MSI by Next-Generation Sequencing (example: mSINGS)

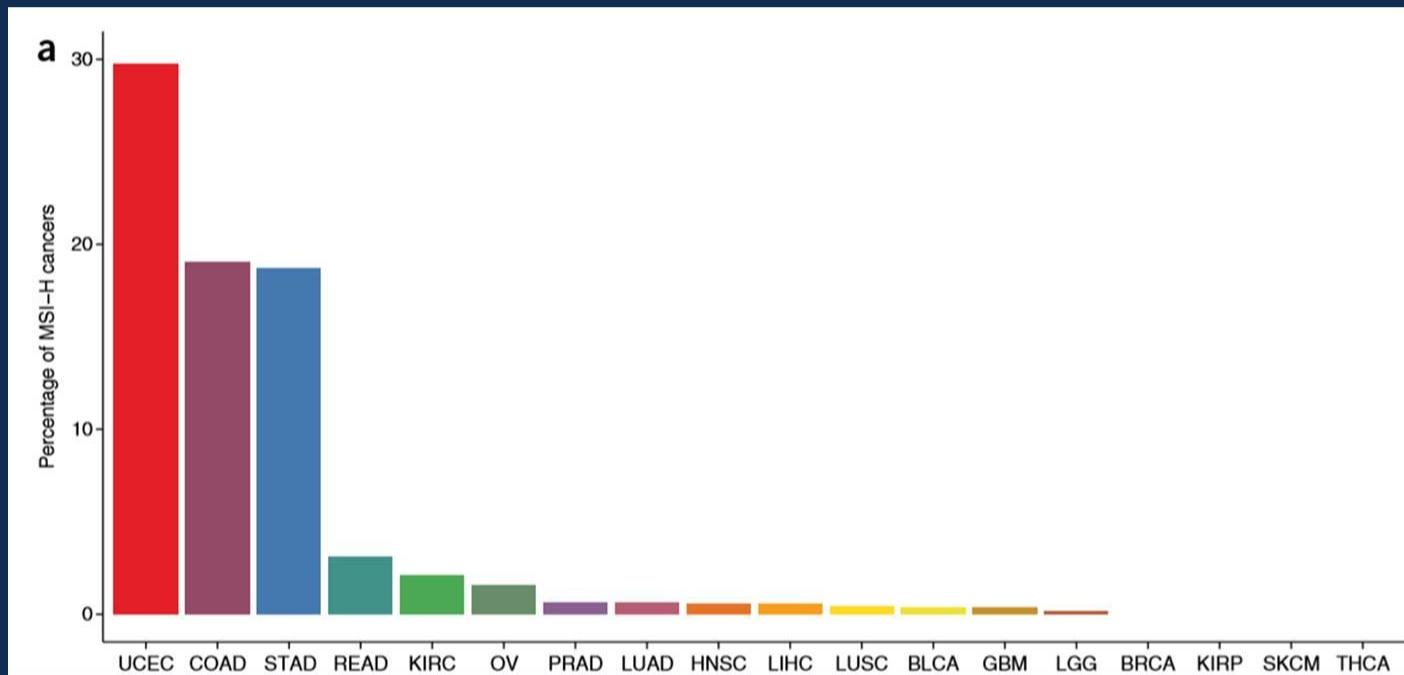


Salipante et al. (2014) *Clinical Chemistry* PMID:24987110

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Landscape of MSI Between Cancers



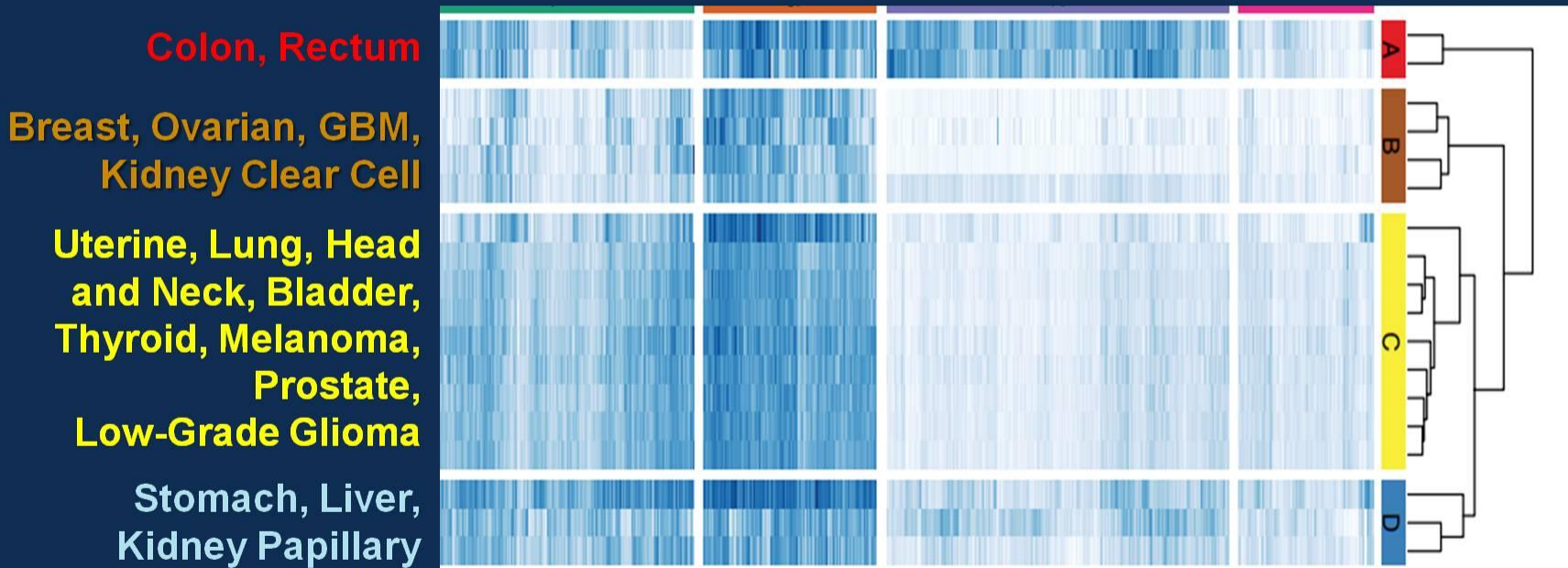
Hause et al. (2016) *Nat. Med.* PMID:27694933

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MSI Patterns Are Not The Same Between Cancer Types



Hause et al. 2016 *Nat. Med.* PMID:27694933

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Why Might Cancer-Specific Differences in MSI Pattern Matter? **False Negatives**

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Comparison of Current MMR Methods

Method	Clinical Availability	Cost	Turnaround Time	Sensitivity
MMR IHC	Wide	Lower	Fast	Only established in for colon cancer
MSI-PCR	Wide	Lower	Slower	Only established in for colon cancer
MSI-NGS	Limited	Moderate	Slower	<i>Likely superior to other methods, more data needed</i>

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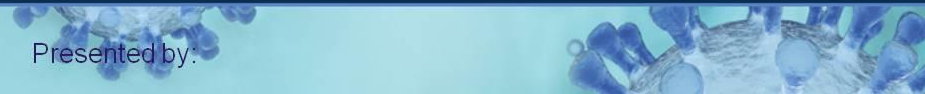
Total Mutation Burden as Biomarker

- Hypermutation correlates well with MMR deficiency
- May capture more PD1/PDL1i responsive cases than MSI
- More data needed
- **Difficult to standardize: Calibration materials needed**

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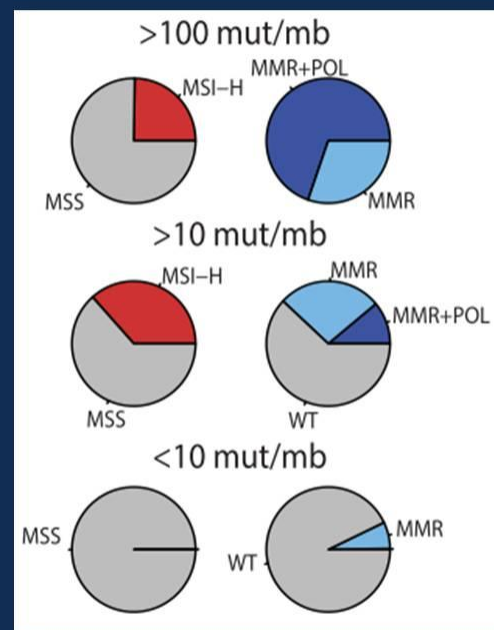


Total Mutation Burden: Mechanisms

Ultramutation: *POLE/POLD1*

Hypermutation: MMR deficiency

Normal/Low Mutation Burden



Campbell et al. (2017) *Cell* PMID: 29056344

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Conclusions/Take-Home Points

- MSI is likely to predict checkpoint blockade responses
- Current **MSI-PCR methods are not well-validated beyond colon cancer**, but are nonetheless being used in many cancer types
- **MSI patterns differ between cancer types**, cancer-tailored MSI methods may be needed to improve sensitivity
- **MSI by NGS is robust and likely superior to traditional methods** due to the large number of loci that can be sampled
- **Total Mutation Burden is a promising biomarker** for checkpoint blockade response, calibrator materials will assist with standardization

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Thank You!

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