11th Annual Advances in Hematology & Oncology
October 29, 2022

Precision Oncology: Challenges and Rewards

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CONQUER CANCER® THE ASCO FOUNDATION

NIH NATIONAL CANCER INSTITUTE

MCW Cancer Center
Pilot Funding Program
MEDICAL COLLEGE OF WISCONSIN CANCER CENTER

Disclosures:

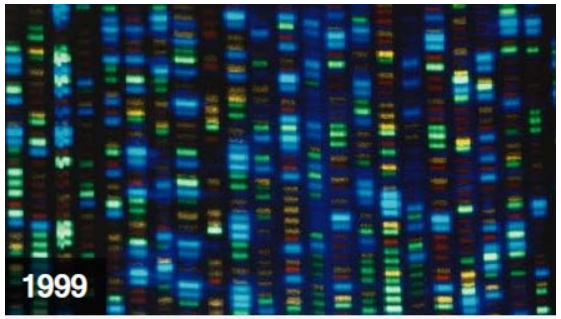
Consultant for Biological Dynamics

Advisory Board PharmaMar

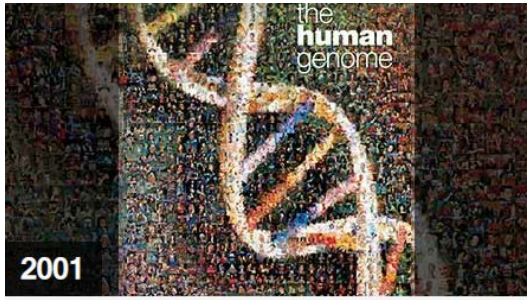
Presentation Outline

- Defining precision medicine
- NCI Precision Medicine Trials
- MCW Rare Cancer and Precision Medicine Clinic
- 2 Case Presentations

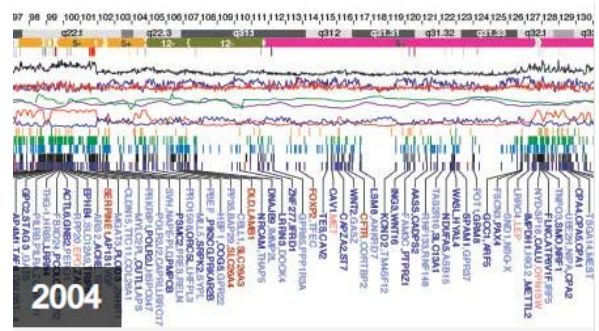
Human Genome Project Timeline



The Human Genome Project successfully completes the pilot phase of sequencing the human genome. **More +**



The International Human Genome Sequencing Consortium publishes an initial analysis of the human genome sequence. **More +**



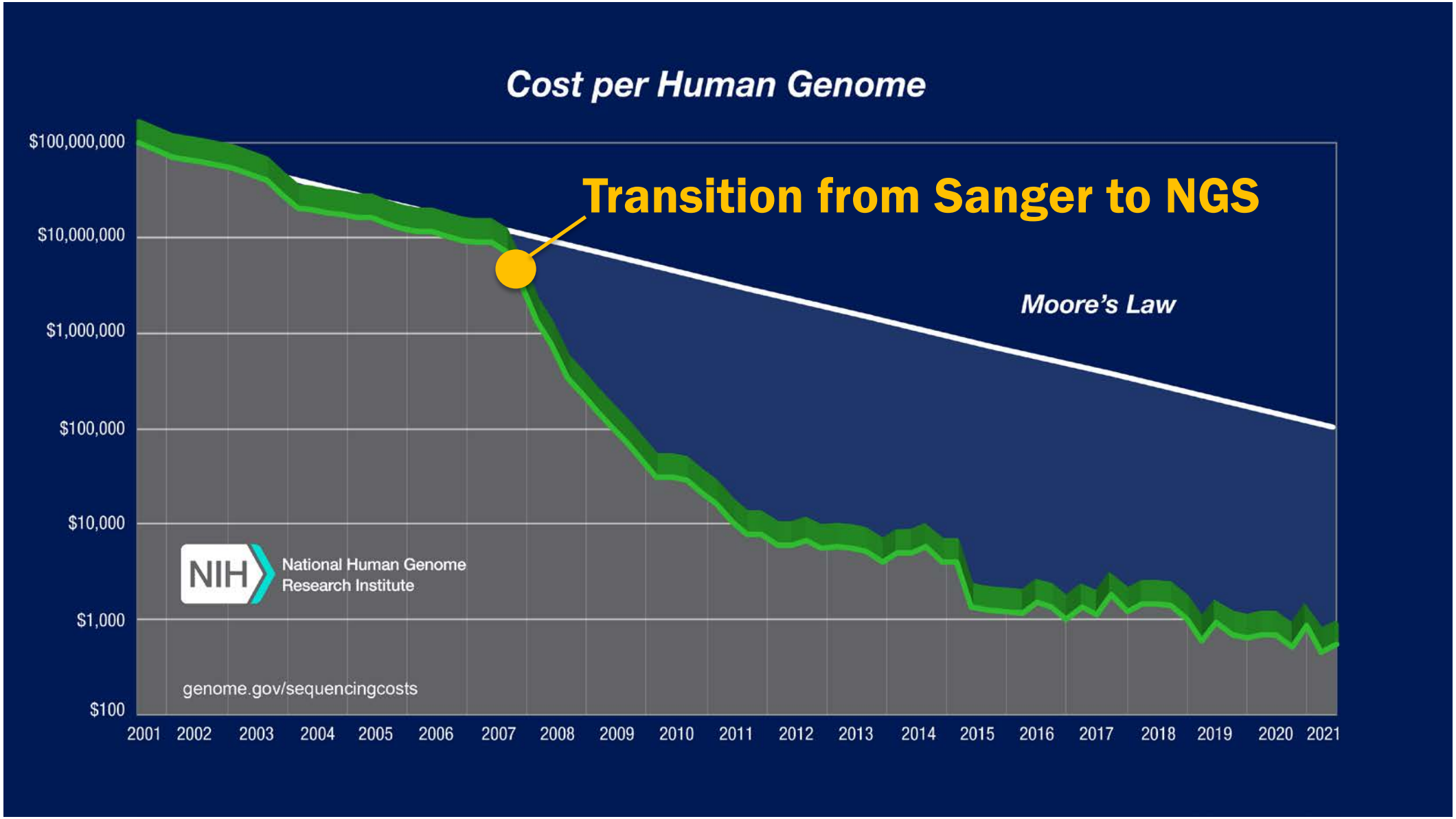
The International Human Genome Sequence Consortium publishes their finished human genome sequence. **More +**

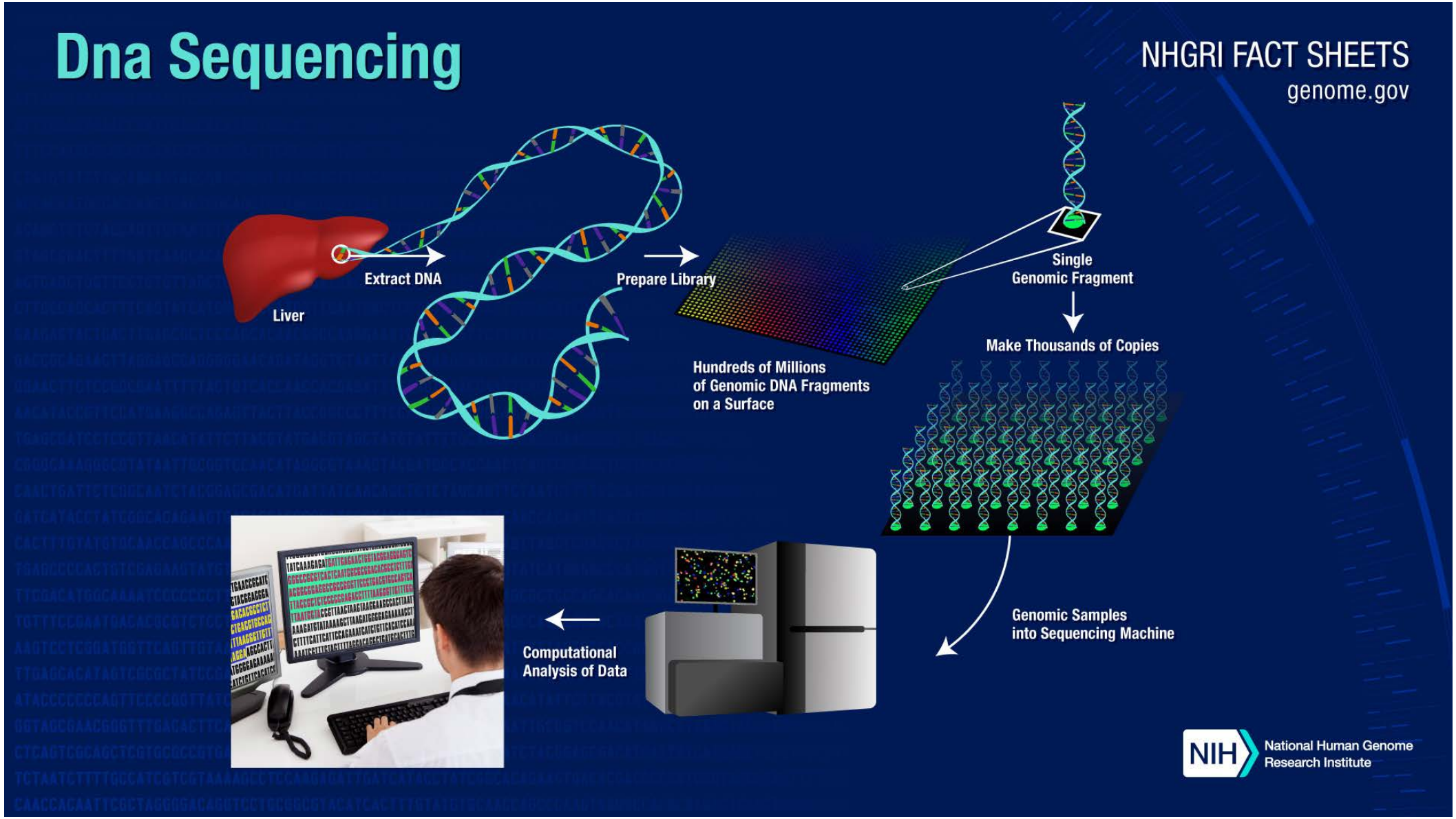
HHS establishes the National Center for Human Genome Research (NCHGR) with James D. Watson** as the first director. **More +**

The International Human Genome Sequencing Consortium announces the completion of a "working draft" human genome sequence. **More +**

The Human Genome Project is completed. **More +**

Projected cost: ~3 billion dollars, 15 years


Cost per Human Genome
Transition from Sanger to NGS
Moore's Law
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts


Dna Sequencing
NHGRI FACT SHEETS
genome.gov
Liver
Extract DNA
Prepare Library
Hundreds of Millions
of Genomic DNA Fragments
on a Surface
Single
Genomic Fragment
Make Thousands of Copies
Genomic Samples
into Sequencing Machine
Computational
Analysis of Data
NIH
National Human Genome
Research Institute

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015

Definition of Precision Medicine

From the National Cancer Institute:

"A form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease"

Evolving Definition of Precision Oncology

"Precision oncology is seductive and appealing.... But like all seductive notions, we must separate evidence supporting a claim from our desire for the claim to be true. In the case of precision medicine, we need clear definitions and criteria for success or failure. We are hoping for success, but there remains much imprecision to this strategy."

Vinay Prasad, MD, MPH, and Robert Peter Gale, MD, PhD, DSc(hc), FACP, FRSM

The ASCO Post

Evolving Definition of Precision Oncology

- **<u>2005-2010:</u> precision oncology predominantly described targeted therapies (e.g. bevacizumab, trastuzumab, imatinib)**

- **<u>2016 and onwards:</u> precision oncology refers to using data from Next-Generation Sequencing (NGS) to guide therapies**

- **Most "paradigm-shifting" definition of precision oncology:**
  - ***Directing therapy independent of cancer type as currently defined (based on anatomy and histology) and instead by gene mutations***

- **2017: first "tissue-agnostic" cancer treatment, pembrolizumab, for any microsatellite instability high (MSI-H) solid tumors**

Current Tissue Agnostic Approvals in Oncology

Therapy	Biomarker	*FDA approval date
Pembrolizumab	MSI-H or dMMR	May 2017
Larotrectinib	NTRK fusion	November 2018
Entrectinib	NTRK fusion	August 2019
Pembrolizumab	TMB-H (≥10 mut/Mb)	June 2020
Dostarlimab-gxly	dMMR	February 2022
Dabrafenib + Trametinib	BRAF V600E	June 2022
Selpercatinib	RET fusion	September 2022

*FDA approved all indications under accelerated approval program, continued approval may hinge upon confirmatory studies.

The Future of Precision Oncology: Multi-omics

"As the first of the omics, genomics revolutionized the diagnosis and treatment of specific diseases. Now that the knowledge of omics has progressed and expanded to include multiple omics (multi-omics), it is not sufficient to solely rely on genomics for personalized treatment plans…"

Multiomics in Precision Medicine
June 2022, Broad Institute (MIT), Boston, MA

The Future of Precision Oncology: Multi-omics

Patient phenotyping

- Tumor biopsy
- Standard clinical analyses
- Tumor omics profiling
- Host omics profiling
- Pharmacogenomics

Patient-directed tx

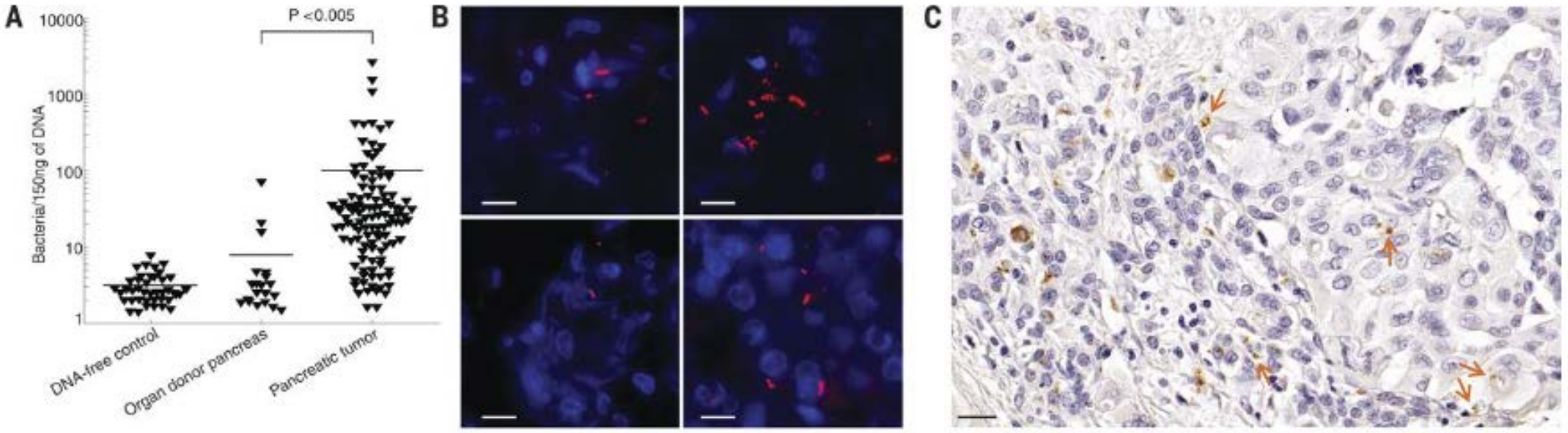
The Future of Precision Oncology: Multi-omics

	Approach	Definition	Common Technologies & Techniques
Tumor	Genomics	Focuses on structure, function, evolution, mapping and editing of information coded within an organism's genome	NGS: WGS, WES, targeted sequencing
Tumor	Epigenomics	How cells control gene activity through non-genetic modifications like DNA methylation and histone modification	NGS: methylation sequencing, ChIP-Seq, ATAC-seq, HiC/3C
Tumor	Transcriptomics	Study of transcriptome, the complete set of RNA transcripts that are produced by genome, and how it is altered in response to regulatory processes, splicing, disease, or other phenomena	NGS: mRNA-seq, whole transcriptome, targeted sequencing
Tumor	Proteomics	Characterize and identify protein expression patterns in response to specific stimuli or following genomic or transcriptomic changes	Mass spectrometry, mass cytometry, NGS-based detection (e.g. CITE-seq, Ab-seq)
Host	Metabolomics	Study of metabolome within cells, biofluids, or tissues to identify and quantify small molecules/metabolites (<1500 Daltons) in a biological system in a high-throughput manner	Nuclear magnetic resonance (NMR) spectrometry and mass spectrometry
Host	Microbiome	Community of microorganisms that live in or on a particular part of body, such as skin or GI tract; dynamic and change in response to exercise, diet, medications and other exposures	NGS: shotgun metagenomic sequencing, 16S rRNA sequencing, microbial metatranscriptomics
Host	Pharmacogenomics	Study of how genes affect a person's response to drugs	Targeted sequencing of genes with high evidence of drug-gene interactions (e.g. Invitae's 38 gene panel)

Bacteria and Cancer: friends or foe?

Science

Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine

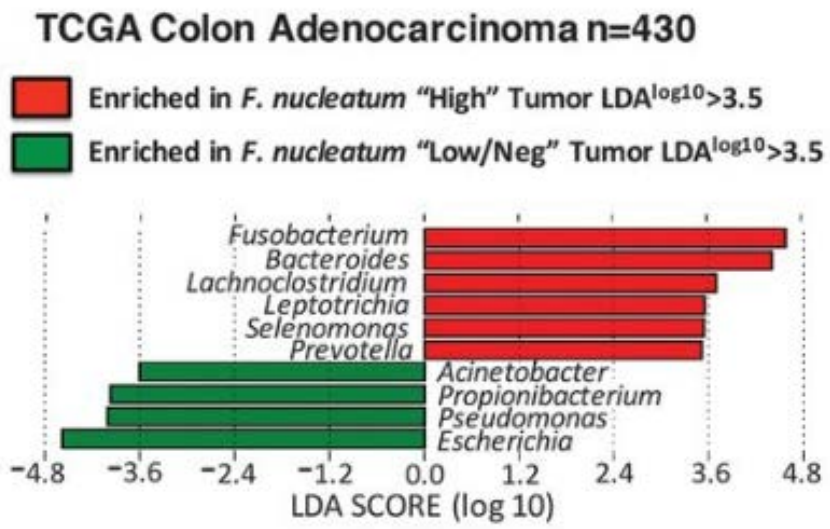


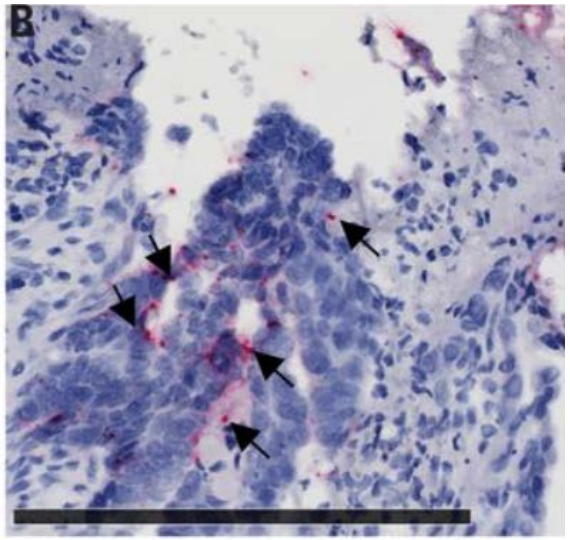
Geller *et al.*, 2017

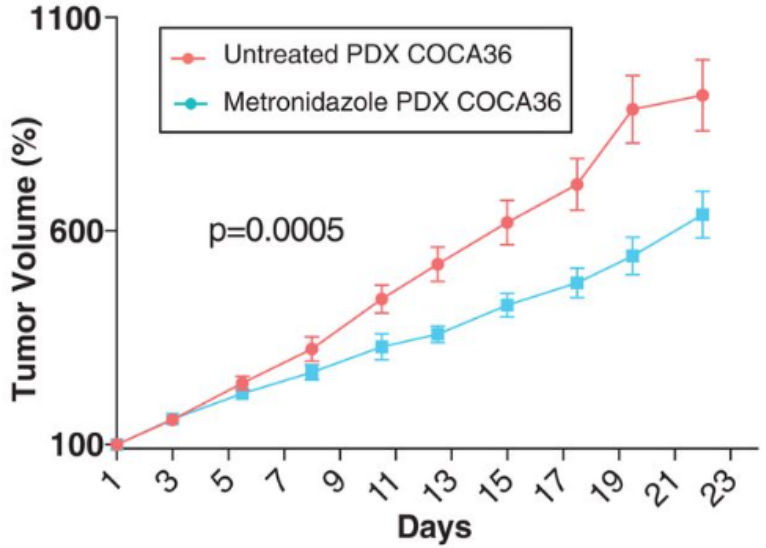
Bacteria and Cancer: friends or foe?

Science

Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer







Bullock *et al.*, 2017

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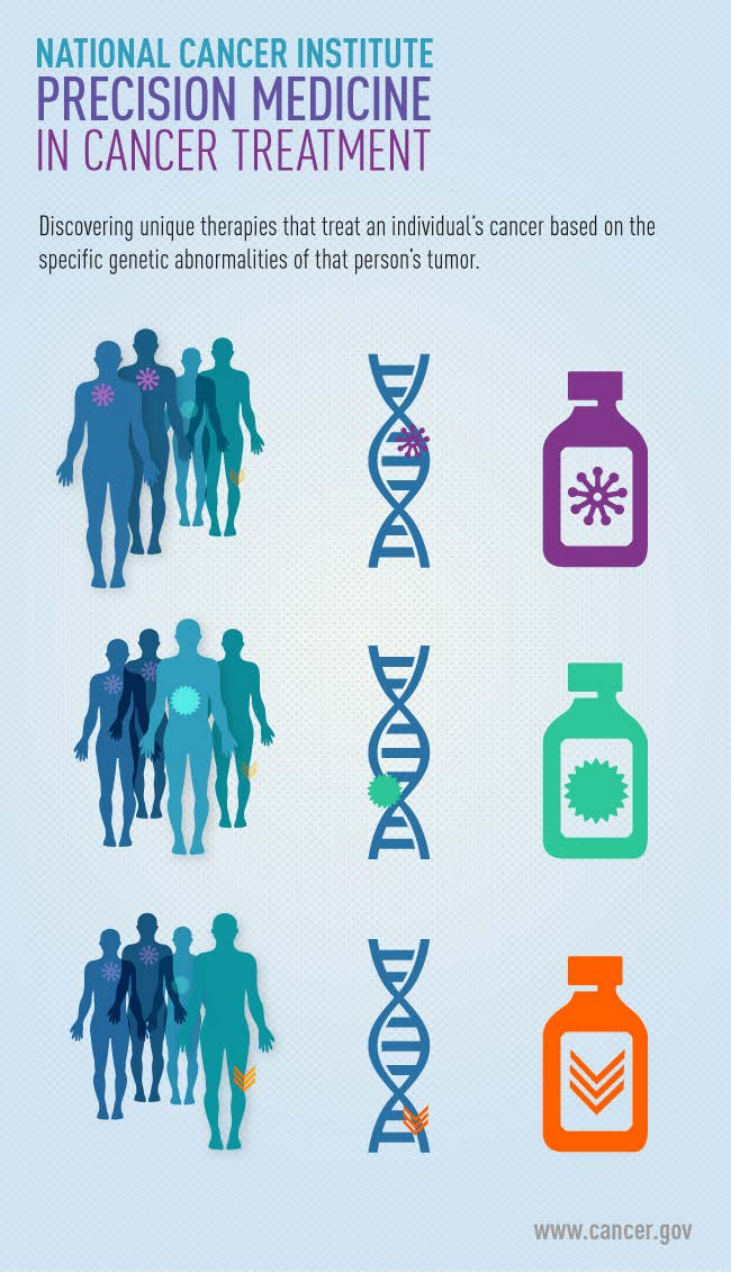
- 2 Case Presentations



NIH Precision Medicine Initiative launched in 2016

- NIH invests $215 million to accelerate biomedical research and provide clinicians with new tools to select individualized therapies for patients

- $70 million for the NCI to advance the field of Precision Oncology, focusing on these key goals:
  - Expanding precision medicine clinical trials
    - Lung cancer master protocol (**Lung-MAP**)
    - Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (**ALCHEMIST**)
    - Molecular Analysis for Therapy Choice (**NCI-MATCH**)
  - Overcoming drug resistance
  - Developing new laboratory models for research
    - NCI Patient-Derived Models Repository
  - Developing a national cancer knowledge system
    - Genomic Data Commons (**GDC**)
    - The Cancer Genome Atlas (**TCGA**): >20,000 primary cancer and matched normal samples sequenced, 33 cancer types; genomic, epigenomic, transcriptomic and proteomic data

THE CANCER GENOME ATLAS

NCI-MATCH: Molecular Analysis for Therapy Choice

NATIONAL CANCER INSTITUTE
NCI-MATCH CLINICAL TRIAL

THIS PRECISION MEDICINE TRIAL EXPLORES TREATING PATIENTS BASED ON THE MOLECULAR PROFILES OF THEIR TUMORS

NCI-MATCH* IS FOR ADULTS WITH:

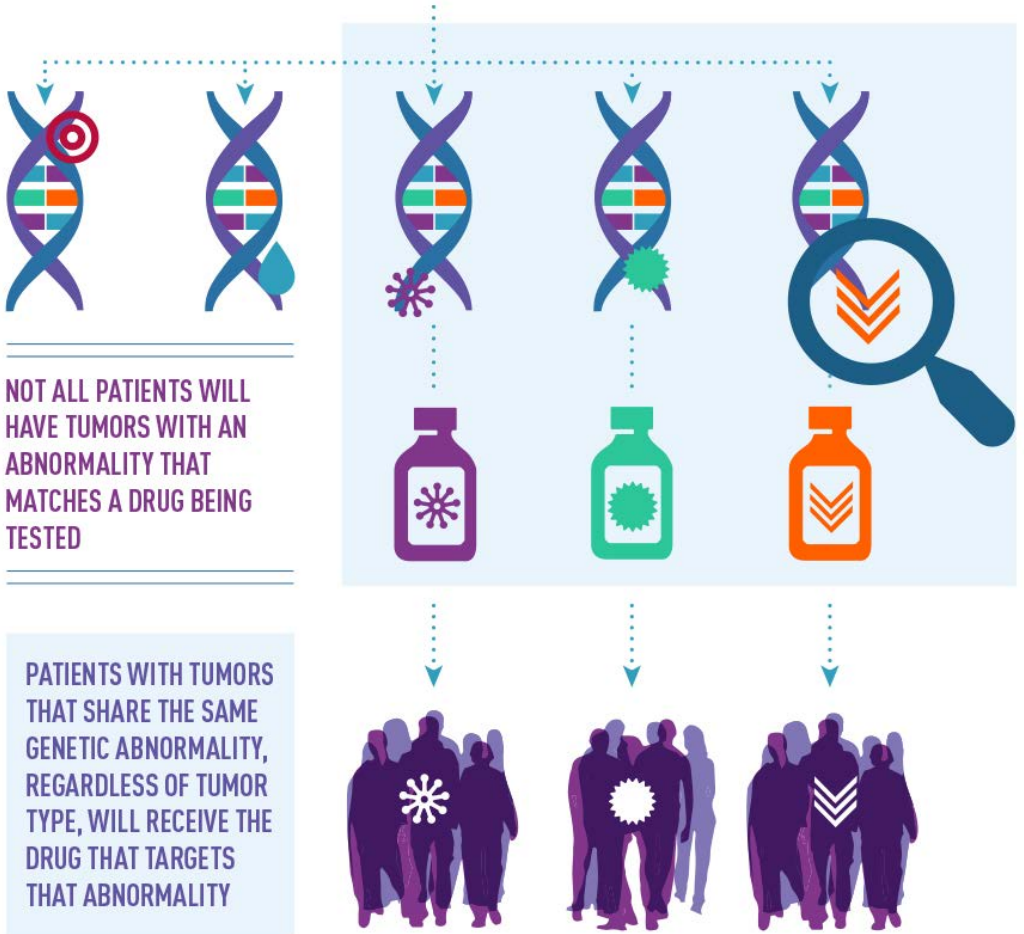
- solid tumors (including rare tumors) and lymphomas
- tumors that no longer respond to standard treatment

ABOUT 3,000 CANCER PATIENTS WILL BE SCREENED WITH A TUMOR BIOPSY

GENE SEQUENCING WILL LOOK FOR CHANGES IN 143 GENES

THE BIOPSIED TUMOR TISSUE WILL UNDERGO GENE SEQUENCING

IF A PATIENT'S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH

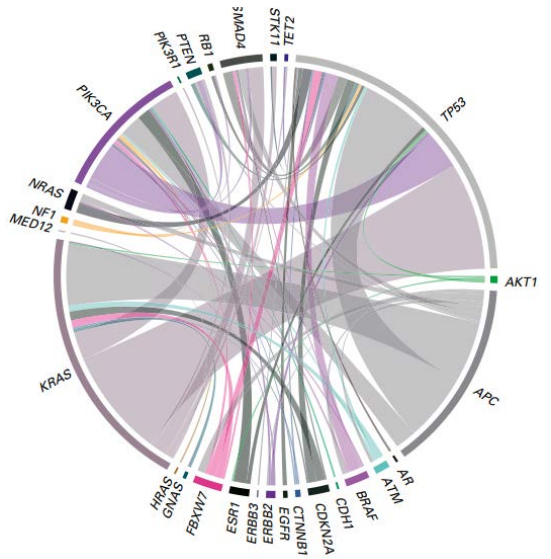


NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY

Journal of Clinical Oncology®

Molecular Landscape and Actionable Alterations in a Genomically Guided Cancer Clinical Trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH)



- **5,954 patients at 1,117 accrual sites analyzed centrally with NGS & selected IHC**
- **Molecular profiling successful in 93.0% of specimens**
- **An actionable alteration was detected in 37.6%**
- **After applying clinical and molecular exclusion criteria, 17.8% were assigned to a subprotocol (total 39?)**
- **Actionability rates differed among histologies (>35% urothelial ca., <6% SCLC)**

Flaherty *et al.*, 2020

Next Generation of NCI NCTN Precision Oncology Trials

- **ComboMATCH (ECOG):** a successor to NCI-MATCH, which tested single drugs
  - Will test combination of targeted drugs in multiple specified patient subgroups supported by preclinical *in vivo* evidence
    - Robust preclinical *in vivo* evidence generated from PDX and CDX data
  - Goal: overcome drug resistance to single-agent therapy, higher RR to combination therapy

- **ImmunoMATCH (SWOG):** in development, master protocol focused on immunotherapy
  - Will perform centralized prospective molecular profiling of all patients based on well validated assays
    - Whole exome sequencing (TMB calculation, somatic variant identification)
    - Gene expression profiling, including generating a tumor inflammation signature
  - Based on results of centralized profiling, patients will be assigned to sub-studies
  - 2-stage pilot study NCT05136196 (cabo/nivo for melanoma and H&N cancer): confirm iMATCH assay platform can deliver results in 21 days

- **MyeloMATCH (SWOG):** soon to launch, umbrella trial to test treatments for AML and MDS
  - Evaluate both targeted and non-targeted agents
  - Evaluate role of MRD in AML

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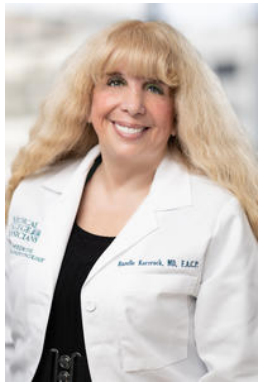
MCW Rare Cancers and Precision Medicine Clinic

Our treatment strategy integrates all aspects of routine oncology care, including but not limited to chemotherapy, radiotherapy and surgery, but *we emphasize genomically guided treatments based on in depth multi-omic and immune profiling of a patient's cancer.*

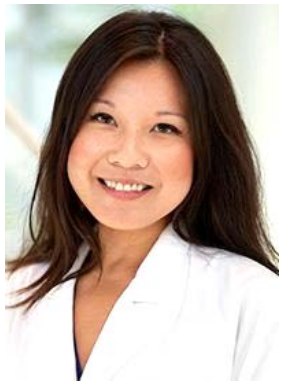
A multidisciplinary team of experts meet weekly at a Molecular Tumor Board to review patient cases in order develop the most personalized and precise treatment plan for each patient.

The treatment plan may include investigational therapies that may be accessed through numerous innovative biomarker driven-clinical trials at the MCW Cancer Center.



Razelle Kurzrock, MD

Aditya Shreenivas, MD MS



Huizi Chen, MD PhD

MCW Rare Cancers and Precision Medicine Clinic

Which patients should be referred?

This clinic is intended to serve unmet needs of the following patients:

1. **Patients with any type of cancer for whom the referring physician believes a precision medicine consult, guided by specialized genomic, transcriptomic, immunomic or functional analysis will be helpful to identify therapies.**

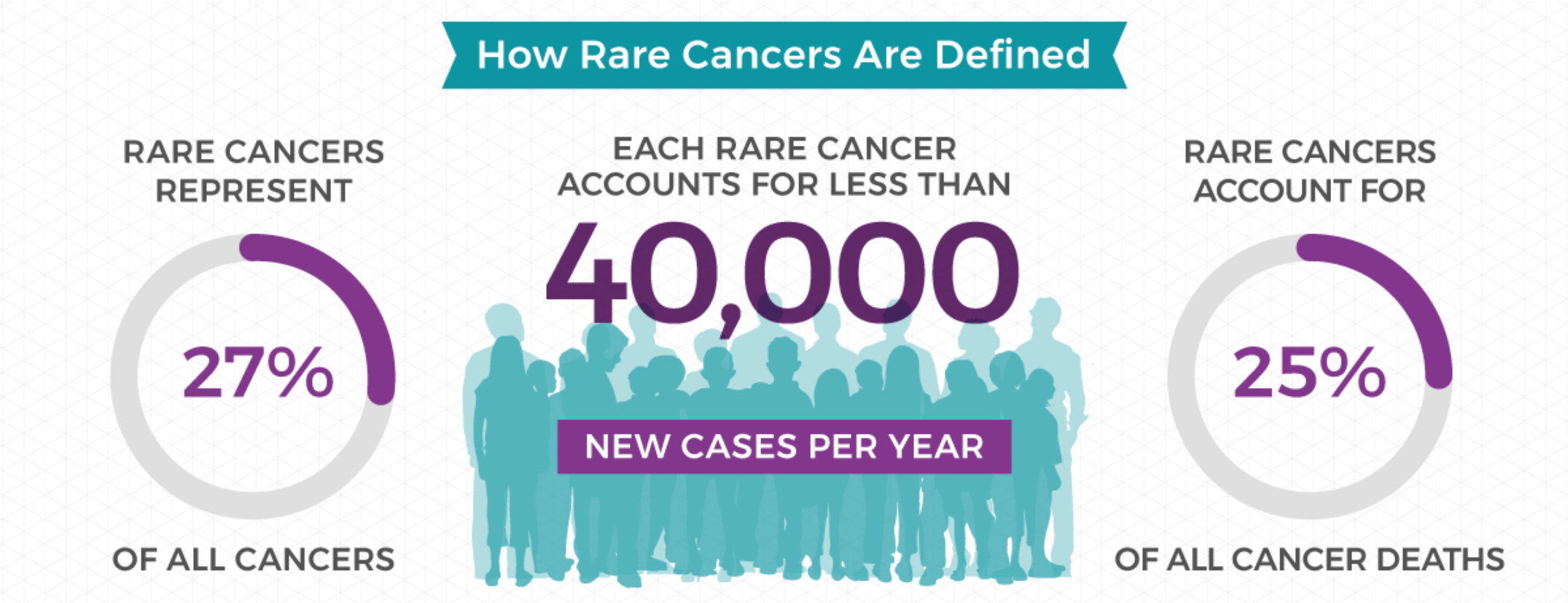
2. **Patients with rare or ultra-rare cancer types.**

American Cancer Society®

https://www.cancer.org/cancer/rare-cancers.html

MCW Rare Cancers and Precision Medicine Clinic

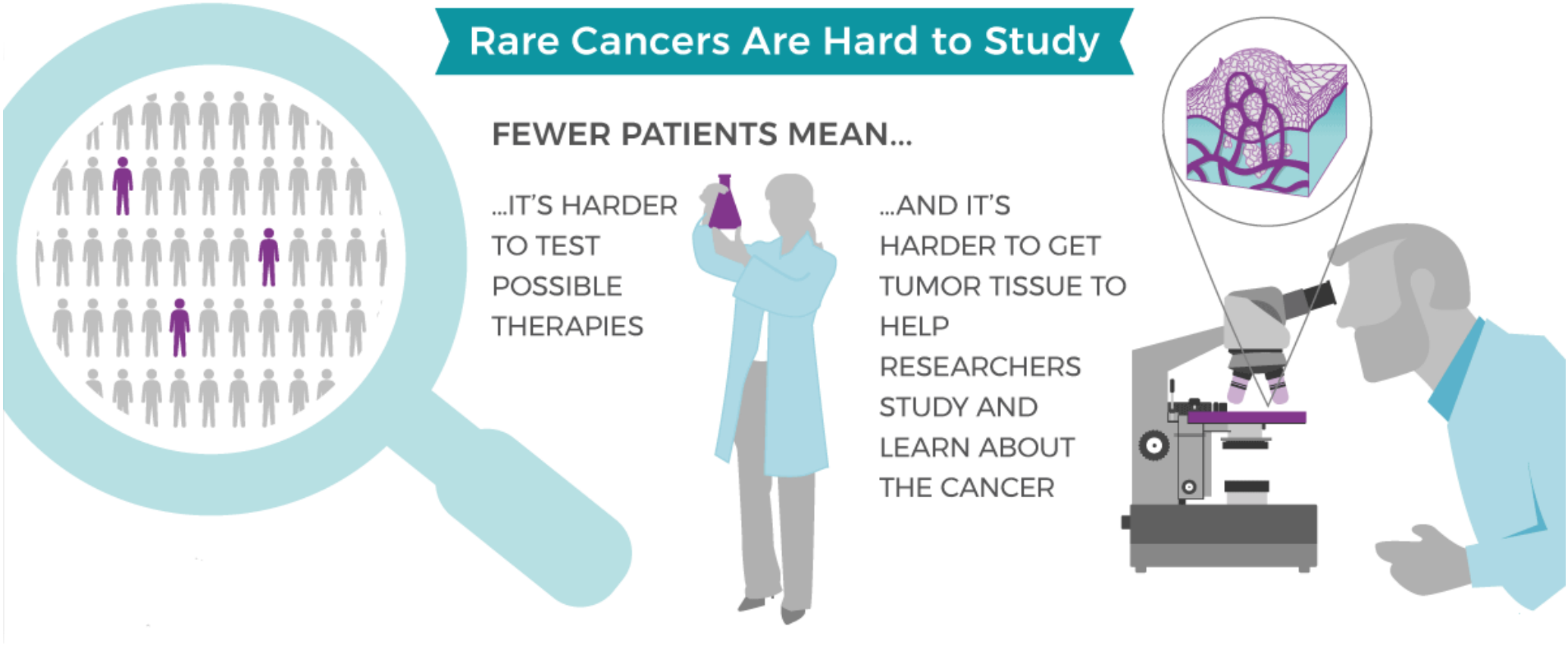
Which patients should be referred?



Incidence: <15 per 100,000 persons each year

MCW Rare Cancers and Precision Medicine Clinic

Which patients should be referred?



MCW Rare Cancers and Precision Medicine Clinic

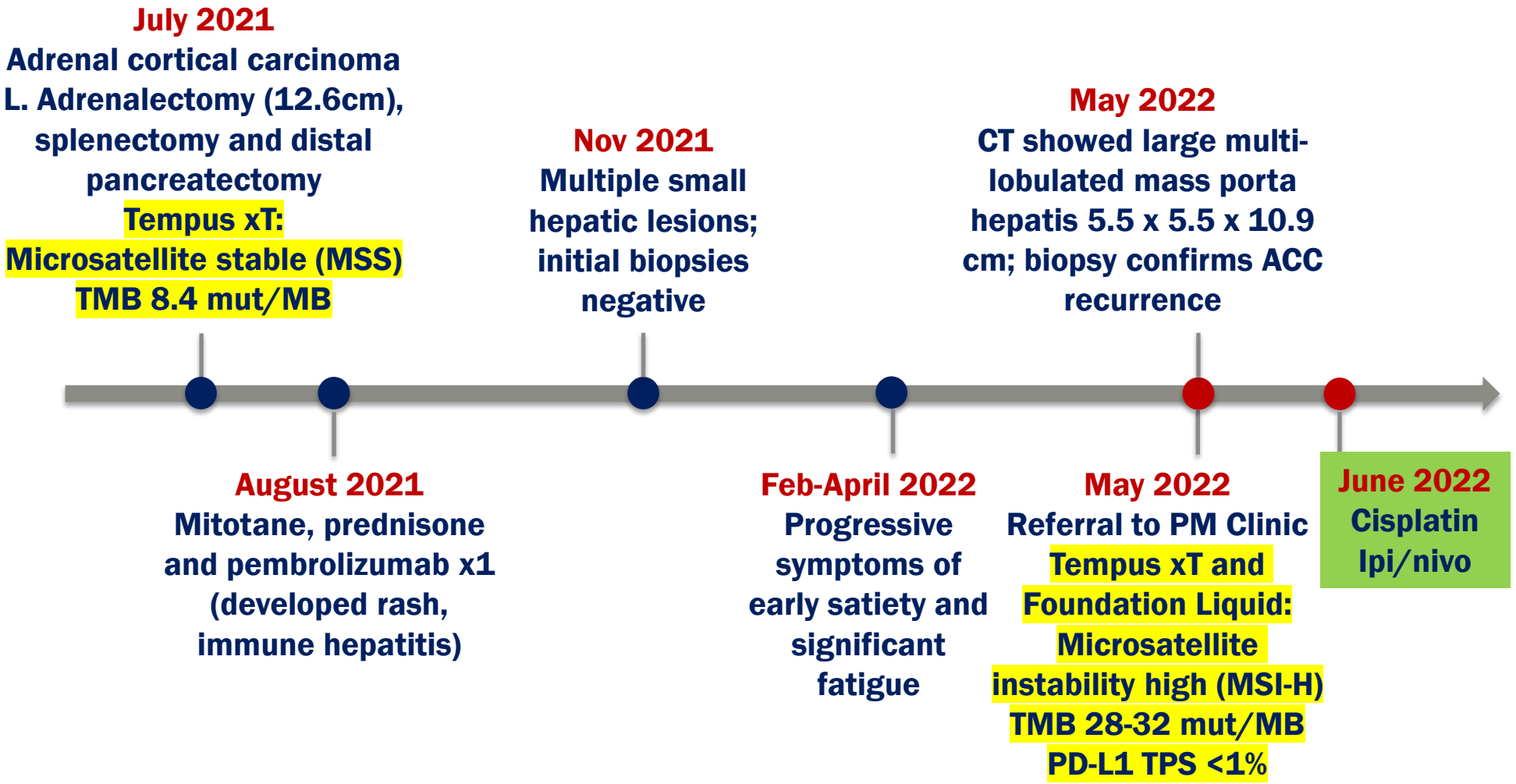
Michels Rare Cancers Research Laboratories

Case presentations

- **41 yo female Lynch Syndrome patient with microsatellite instability high (MSI-H) adrenal cortical cancer**
  - **Autosomal dominant inheritance cancer predisposition syndrome**
  - **Lifetime risk estimates:**
    - **52-82% colorectal cancer**
    - **25-60% endometrial cancer**
    - **6-13% stomach cancer**
    - **4-12 ovarian cancer**
    - **Increased risk of prostate cancer**
  - **Germline *MLH1* pathogenic mutation c.677+3A>G (Ambry Genetics)**
  - **Mutation associated with exon skipping, premature protein truncation, lack of full-length transcript production from variant allele (MLH1 IHC negative)**

- **57 yo renal cell carcinoma male patient with somatic *VHL* and *PTEN* mutations**

MSI-H Adrenal Cortical Cancer arising in Lynch Syndrome Patient



July 2021 Tempus xT

GENOMIC VARIANTS

Biologically Relevant			Variant Allele Fraction
MEN1	p.R516fs	Frameshift - LOF	84.7%
RNF43	p.G659fs	Frameshift - LOF	82.0%
TP53	p.G245S	Missense variant - LOF	81.4%
ATRX	p.E886fs	Frameshift - LOF	75.5%
KMT2C (MLL3)	p.K2797fs	Frameshift - LOF	40.2%

Germline - Pathogenic / Likely Pathogenic

No matched normal sample was received, therefore germline sequencing was not performed.

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

8.4 m/MB 84th percentile

Microsatellite Instability Status

Stable | Equivocal | High

May 2022 Tempus xT

GENOMIC VARIANTS

Potentially Actionable			Variant Allele Fraction
CHEK1	p.T226fs	Frameshift - LOF	39.8%

Biologically Relevant			
RNF43	p.G659fs	Frameshift - LOF	85.1%
MEN1	p.R516fs	Frameshift - LOF	82.5%
NF1	p.Y628fs	Frameshift - LOF	81.7%
ATRX	p.E886fs	Frameshift - LOF	80.8%
TP53	p.G245S	Missense variant - LOF	80.6%
JAK1	p.L431fs	Frameshift - LOF	80.5%
FLCN	p.H429fs	Frameshift - LOF	45.6%
KMT2D	p.L2331fs	Frameshift - LOF	44.7%
KMT2D	p.K3140fs	Frameshift - LOF	41.4%
CHD2	p.V175fs	Frameshift - LOF	38.1%
CREBBP	p.Q986*	Stop gain - LOF	33.3%

Germline - Pathogenic / Likely Pathogenic

No matched normal sample was received, therefore germline sequencing was not performed.

Many potential neoantigens!

IMMUNOTHERAPY MARKERS

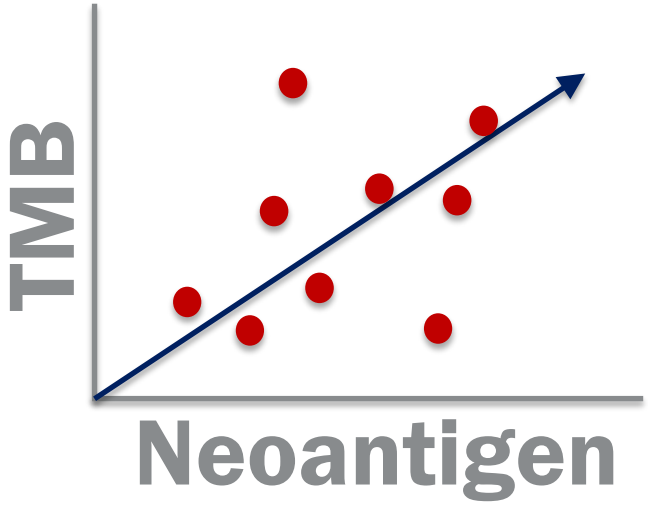
Tumor Mutational Burden

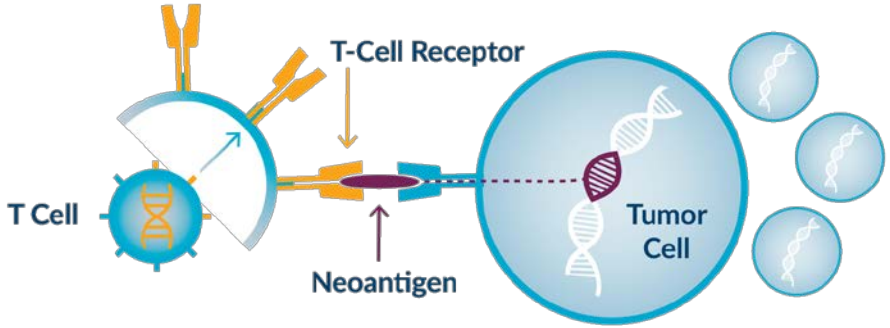
28.4 m/MB 97th percentile

Microsatellite Instability Status

Stable | Equivocal | High

Frameshift indels generate more tumor-specific neoantigens than point mutations: indels offer “more bang for your buck”





Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis

	Mutations (n)	Neoantigens (n)*	Mutant-specific neoantigens (n)†	Neoantigens per mutation	Mutant-specific neoantigens per mutation
nsSNVs	335 594	214 882	75 224	0·64	0·22
fs-indels	19 849	39 768	39 608	2·00	2·00
Enrichment	..	..	..	3·13	8·94

nsSNVs=non-synonymous single nucleotide variants. fs-indels=frameshift insertions and deletions. *Strong binders (<50 nM affinity). †Wild-type allele non-strong binding (>50 nM affinity).

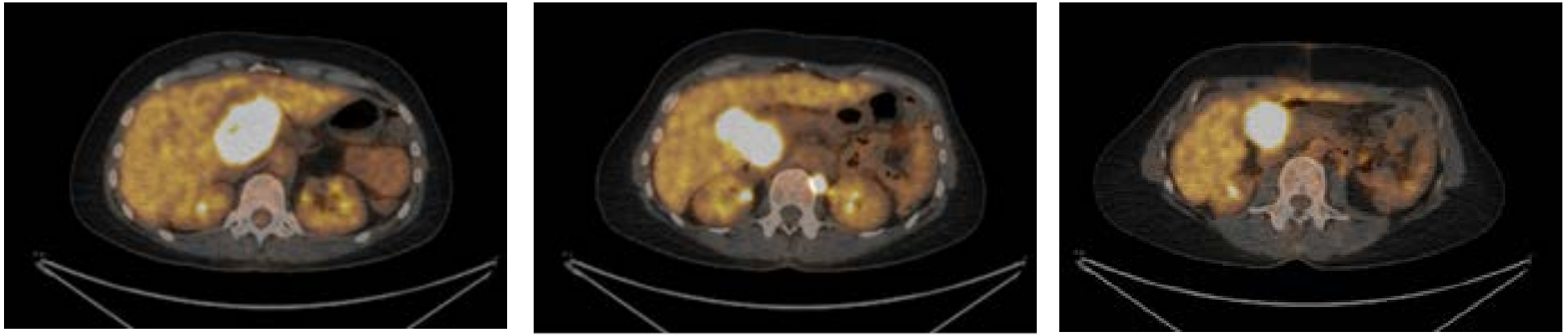
Table: Neoantigens per variant class

FS indel load was more strongly associated with response to ICI than nsSNV load in 3 independent melanoma cohorts

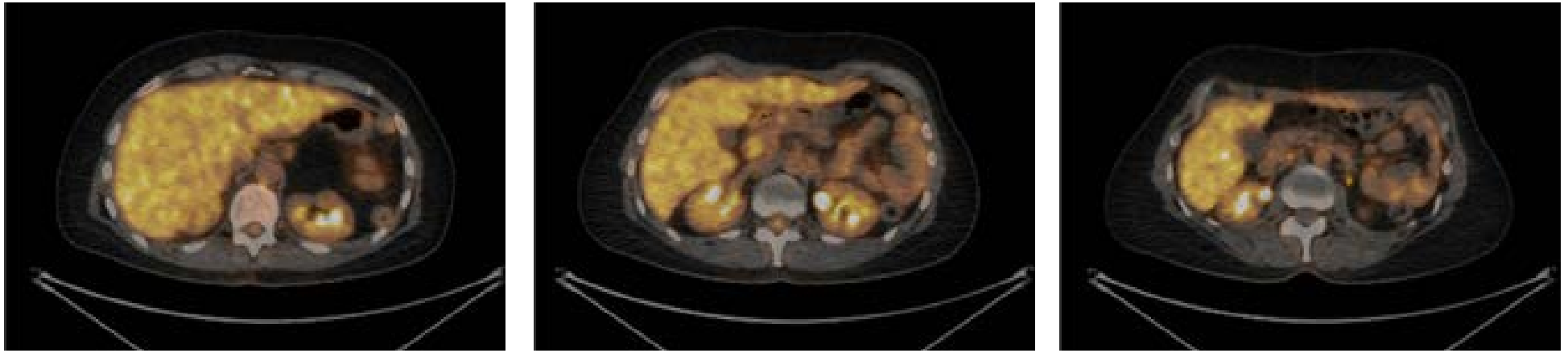
Lancet Oncology 2017

MSI-H Adrenal Cortical Cancer arising in Lynch Syndrome Patient

May 2022 Pre-Tx



August 2022 Ipi/nivo

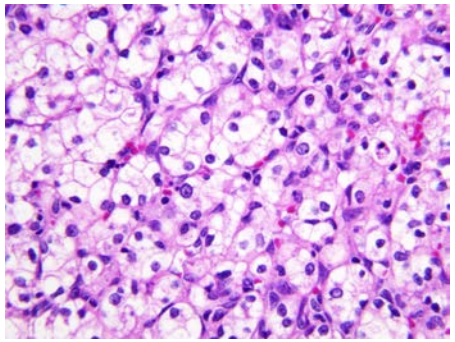


Fortunately no evidence of immune dermatitis or hepatitis with ipi/nivo!

Renal Cell Carcinoma Patient with Somatic VHL Mutation

June 2016
L. Nephrectomy
(pT3bN0M0)
(SWOG 0931)

July 2017
Metastatic recurrence
RUL lesion → VATS



Oct 2017
PD lung
metastases

Nov 2017
Sunitinib

Feb 2019
Ipi/nivo x4 PR
Severe colitis
Surveillance

Aug 2020
Brain mets
GK SRS to 5 new
brain lesions
Restart nivolumab

Mar 2021
+Cabozantinib

Feb 2022
+Tivosanib

April 2022
Progression
Referral to PM Clinic

April 2022
Foundation Cdx

June 2022
Belzutifan
Everolimus

Genomic Findings

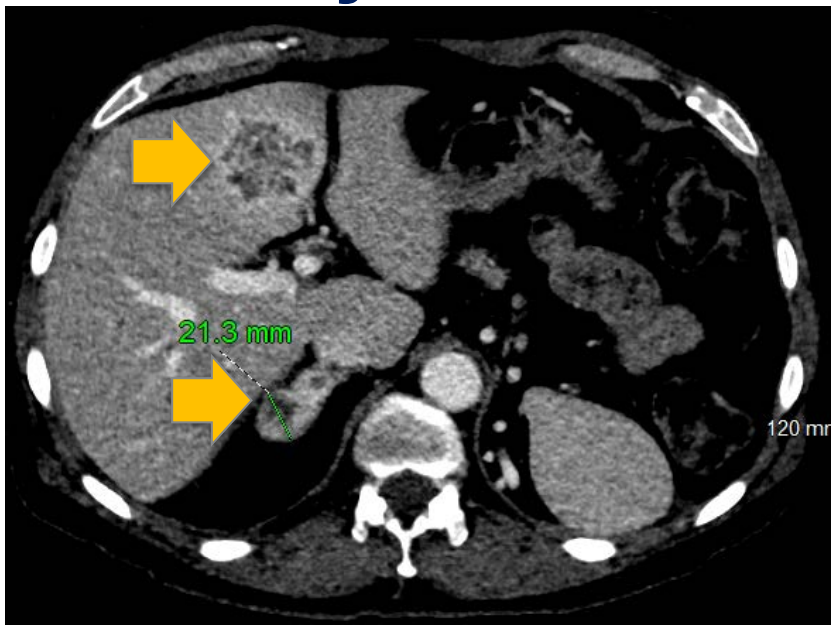
For a complete list of the genes assayed, please refer to the Appendix.

PBRM1 N198fs*26
VHL G114C
APC R876*
FANCA loss exons 19-20
PTEN F90fs*2
EPHA3 amplification - equivocal†
SETD2 Y2296fs*73

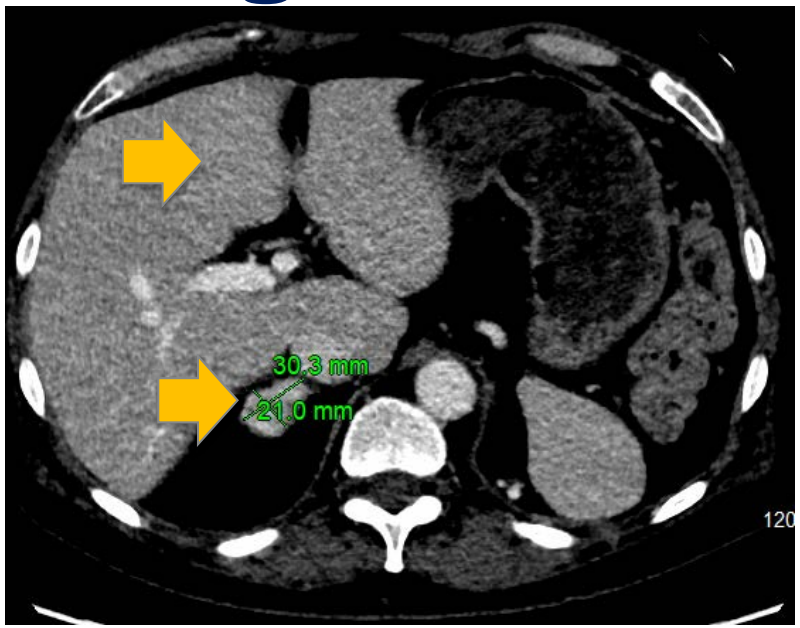
PD-L1 TPS <1%
TMB low (1 mut/Mb)
Microsatellite stable

Renal Cell Carcinoma Patient with Somatic VHL Mutation

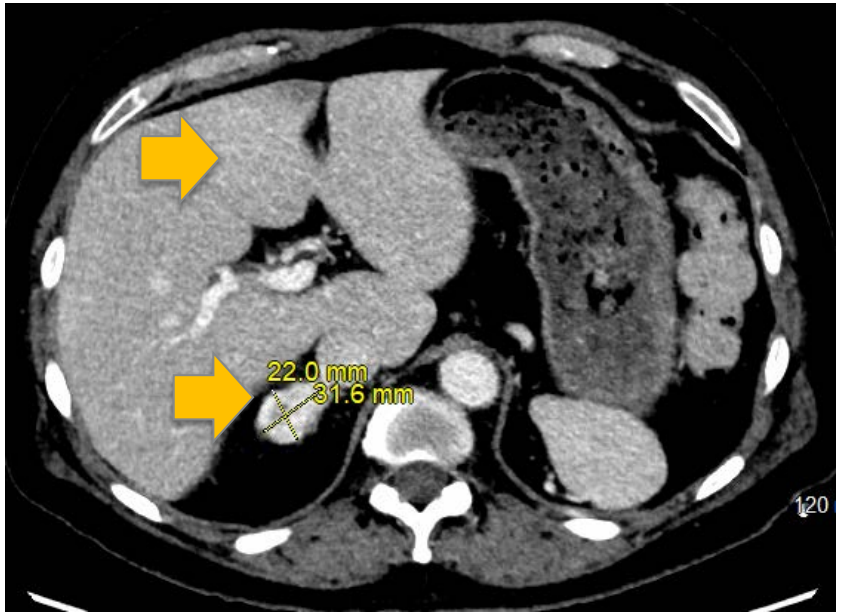
May 2022



August 2022

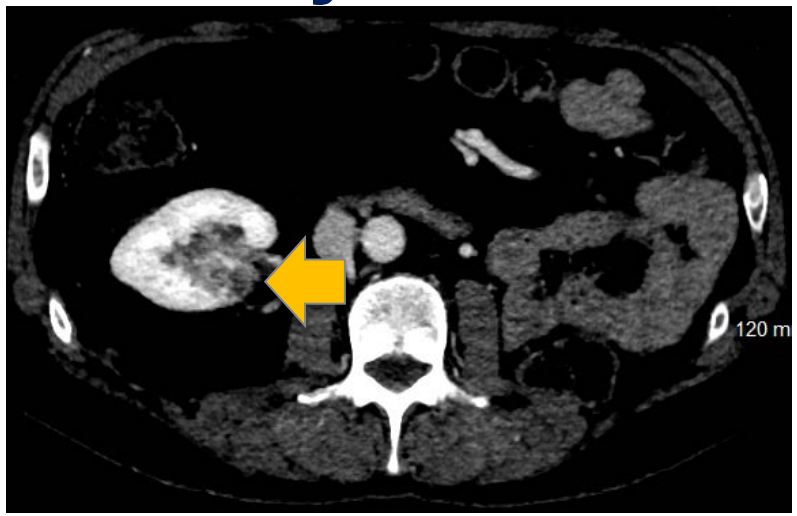


October 2022

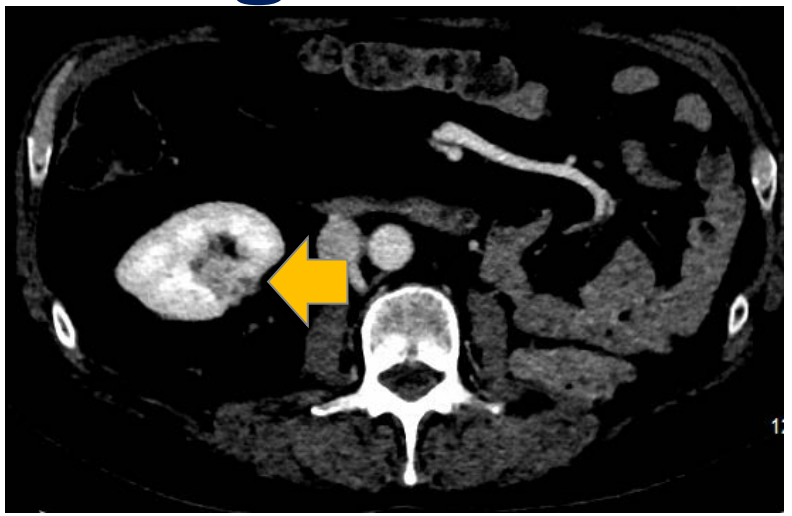


Renal Cell Carcinoma Patient with Somatic VHL Mutation

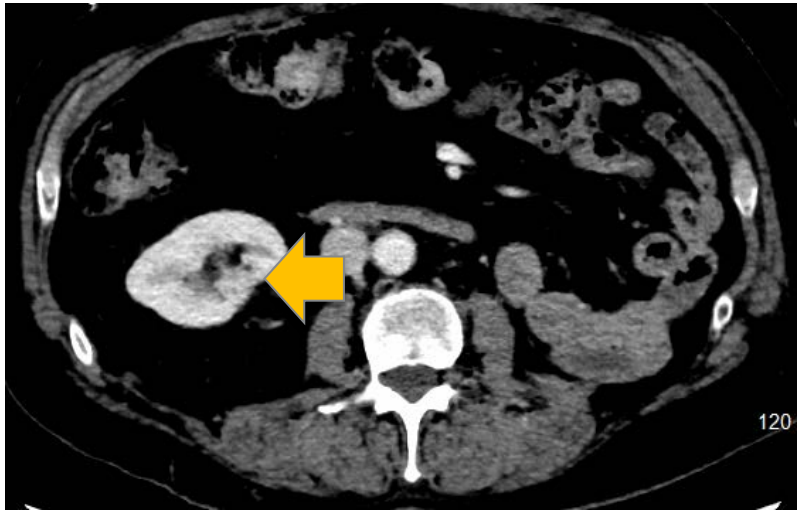
May 2022



August 2022



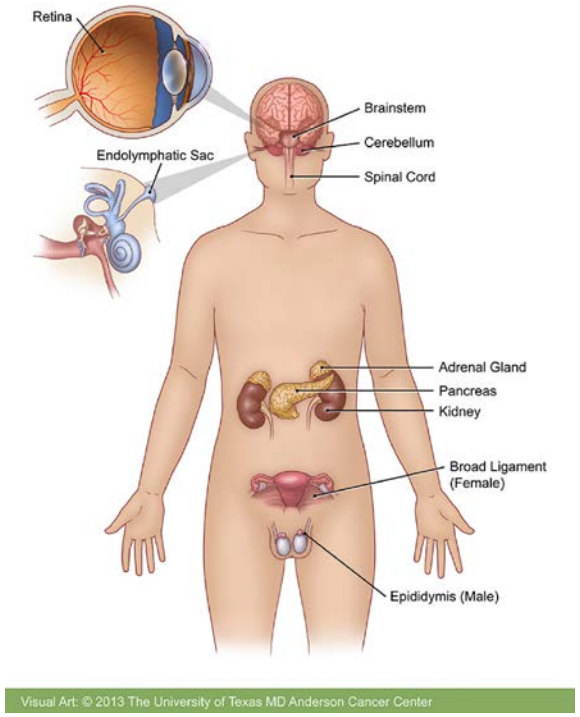
October 2022

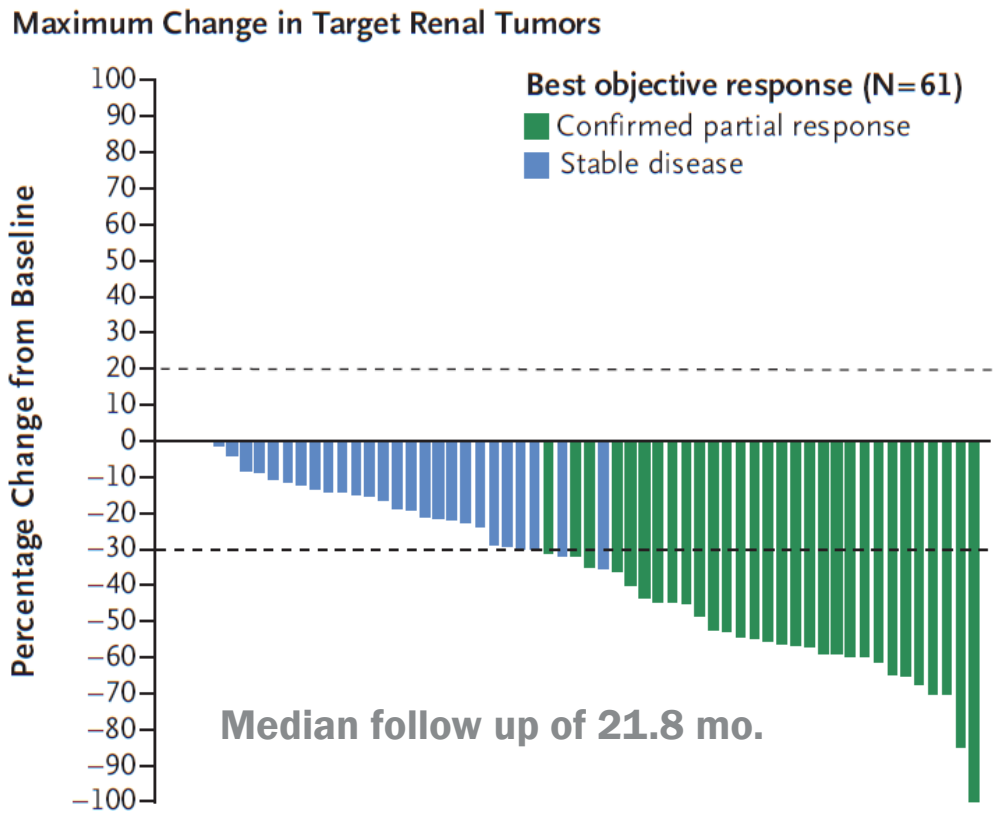


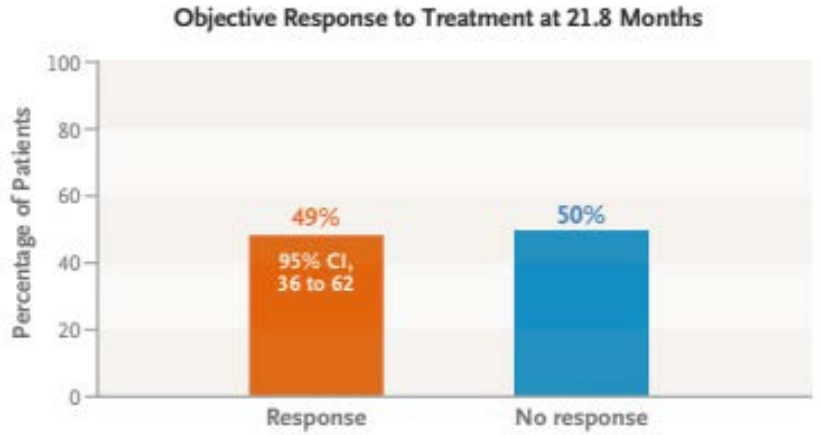
The NEW ENGLAND JOURNAL of MEDICINE

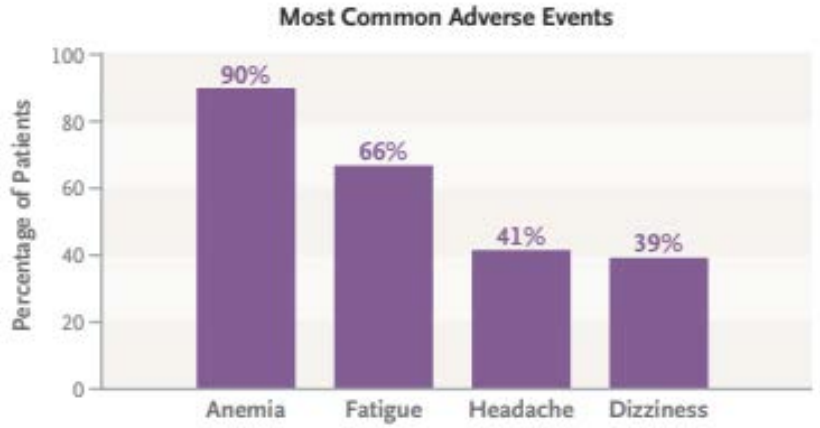
Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Eric Jonasch, M.D., Frede Donskov, M.D., Ph.D., Othon Iliopoulos, M.D., W. Kimryn Rathmell, M.D., Ph.D., Vivek K. Narayan, M.D., Benjamin L. Maughan, M.D., Stephane Oudard, M.D., Tobias Else, M.D., Jodi K. Maranchie, M.D., Sarah J. Welsh, M.D., Sanjay Thamake, Ph.D., Eric K. Park, M.D., et al., for the MK-6482-004 Investigators*

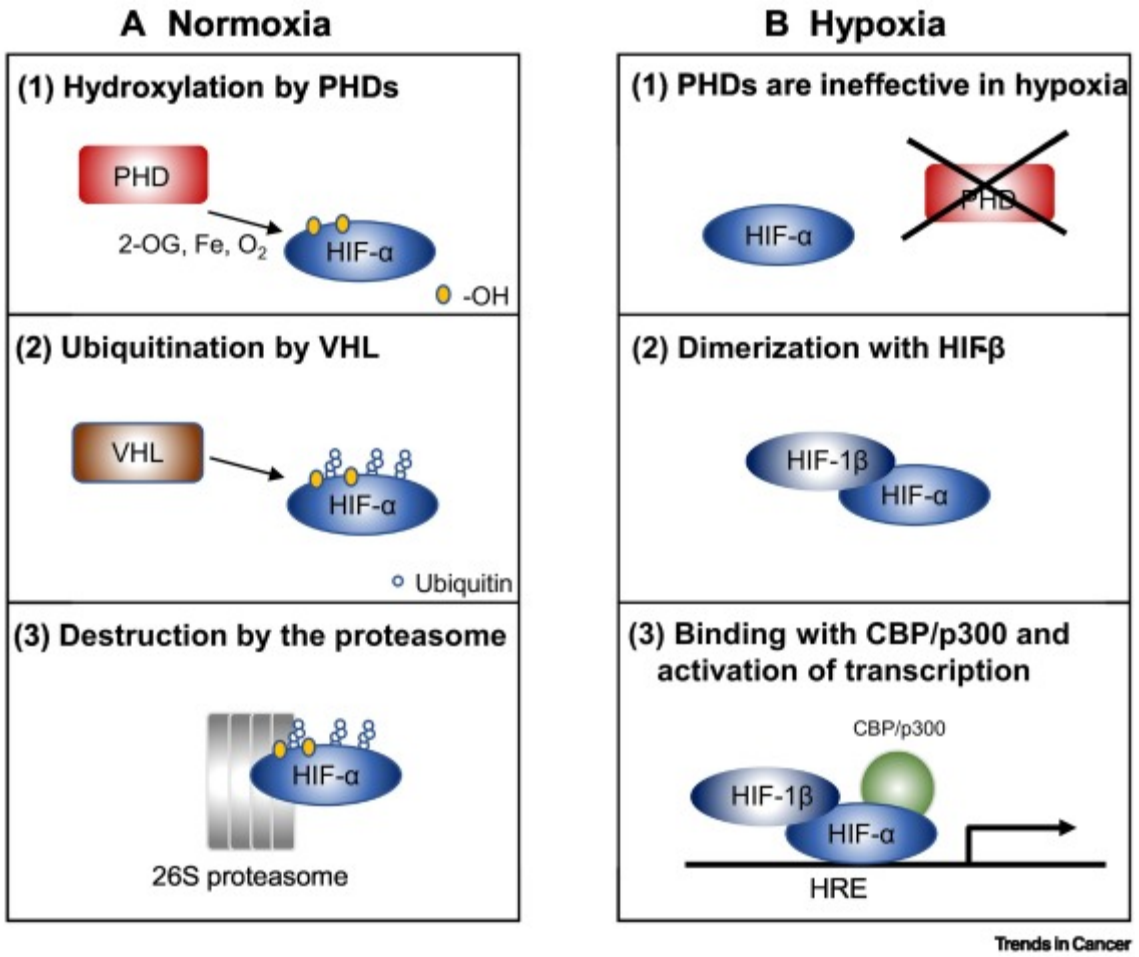


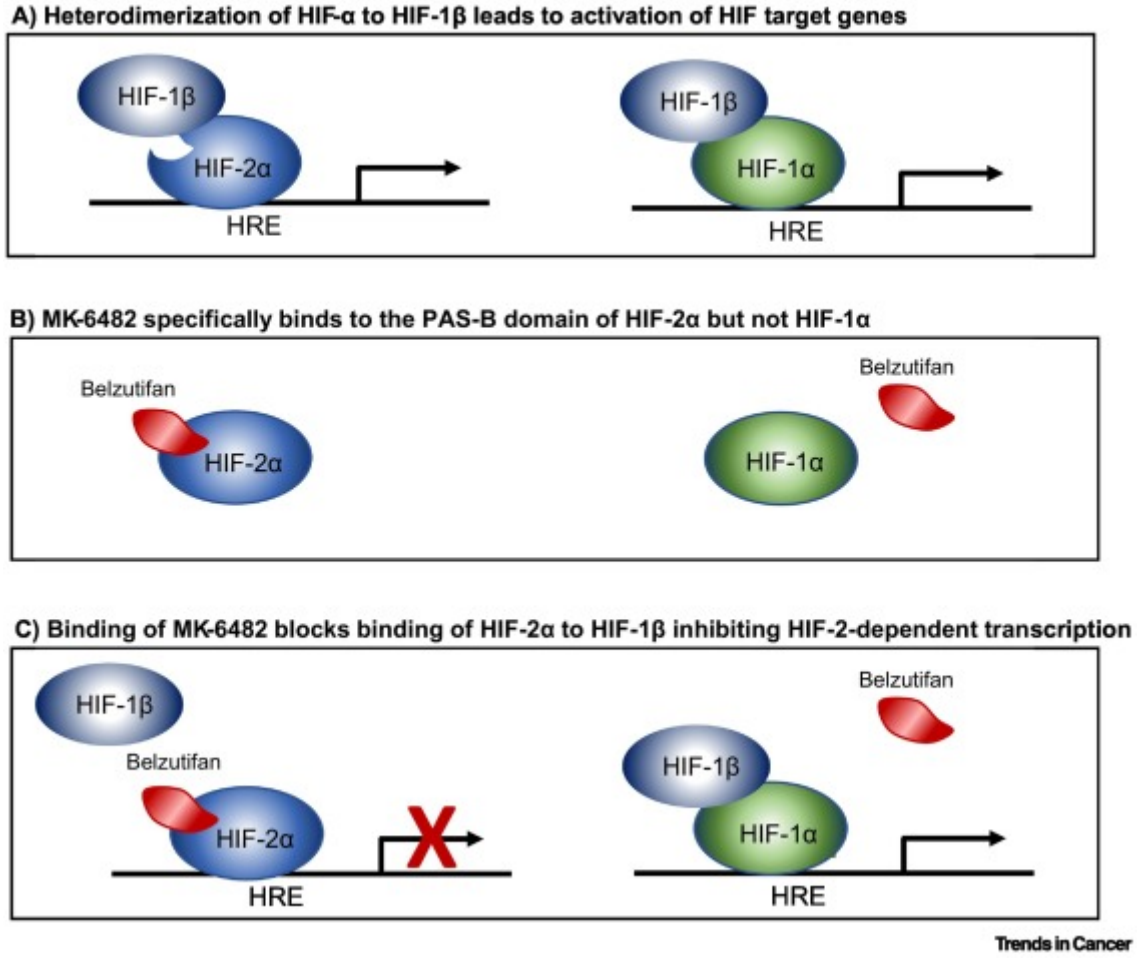






Renal Cell Carcinoma Patient with Somatic VHL Mutation



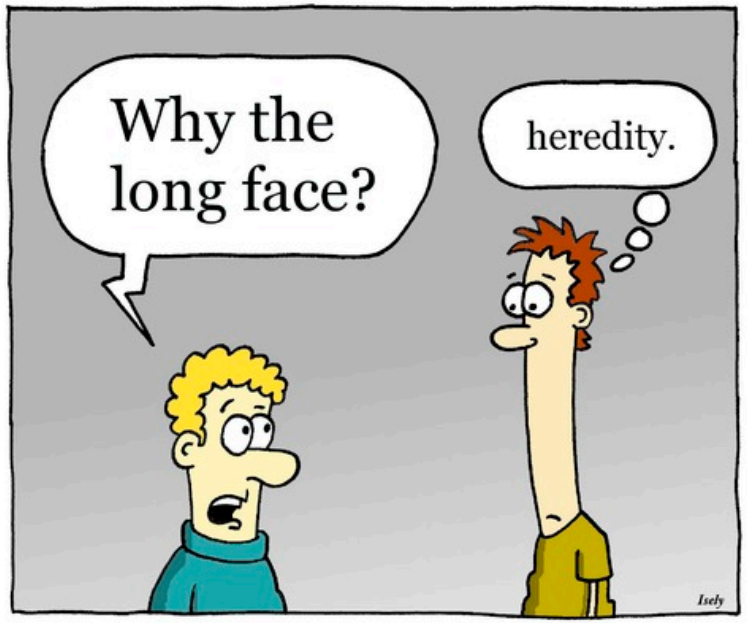


Cowman and Coh, Trends in Cancer 2022


Precision oncology

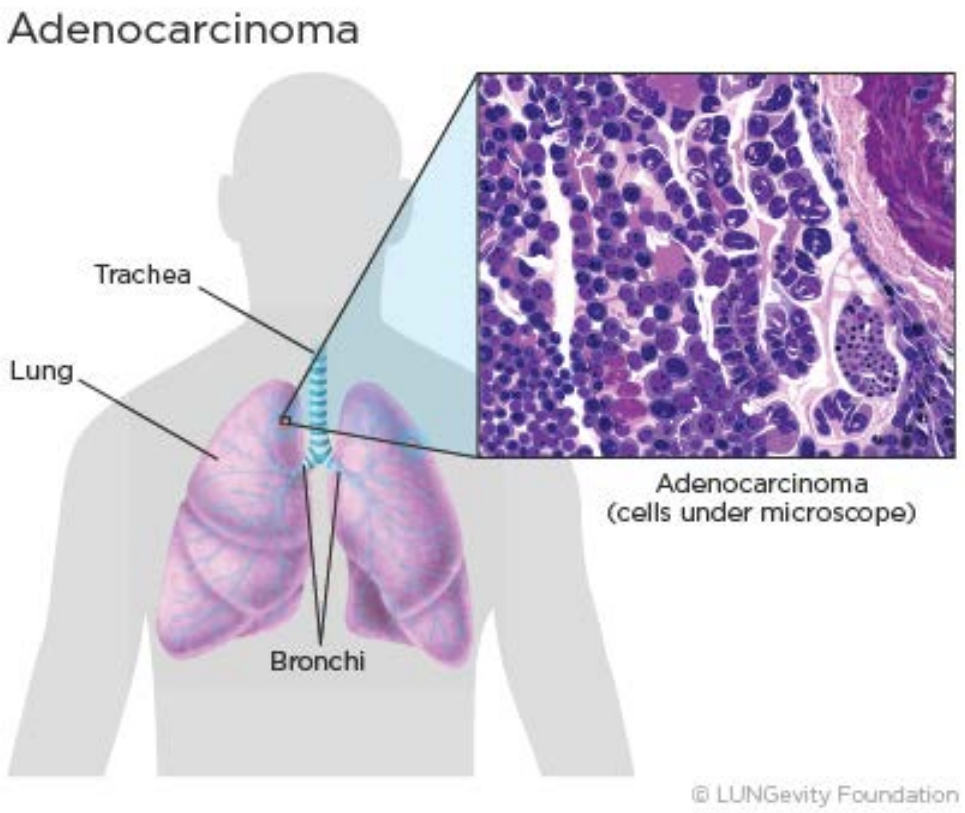
11th Annual Advances in Hematology & Oncology
October 29, 2022

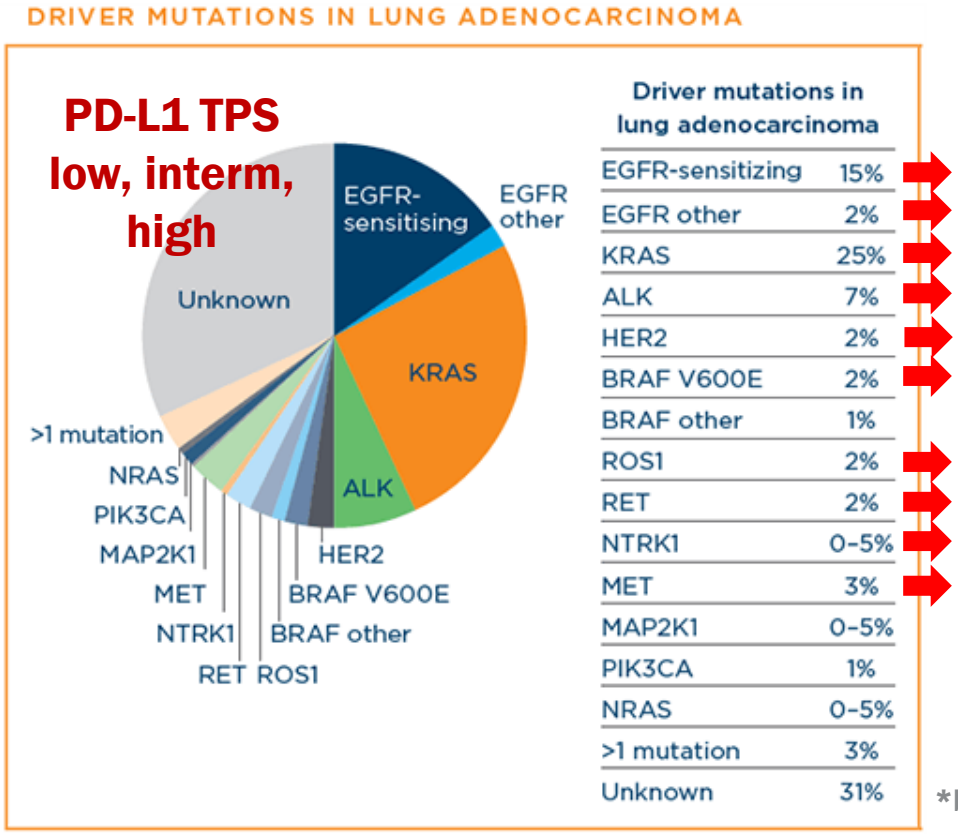
Thank you for your attention!



https://sulishealth.com/
https://sixthperiodgenetics.weebly.com/dna-and-inheritance.html

Non-small cell lung cancer: paradigm of precision oncology

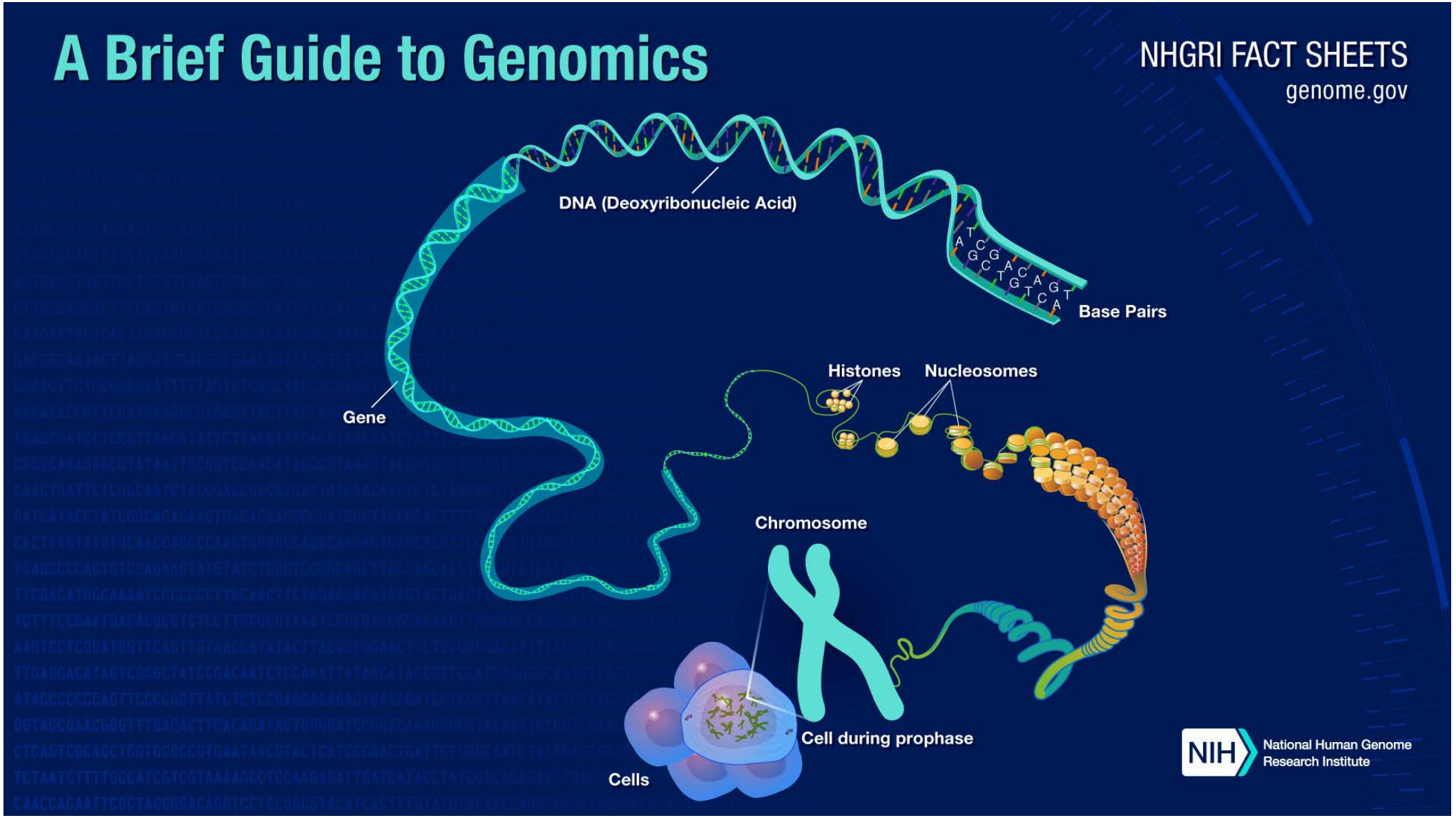




FDA approved

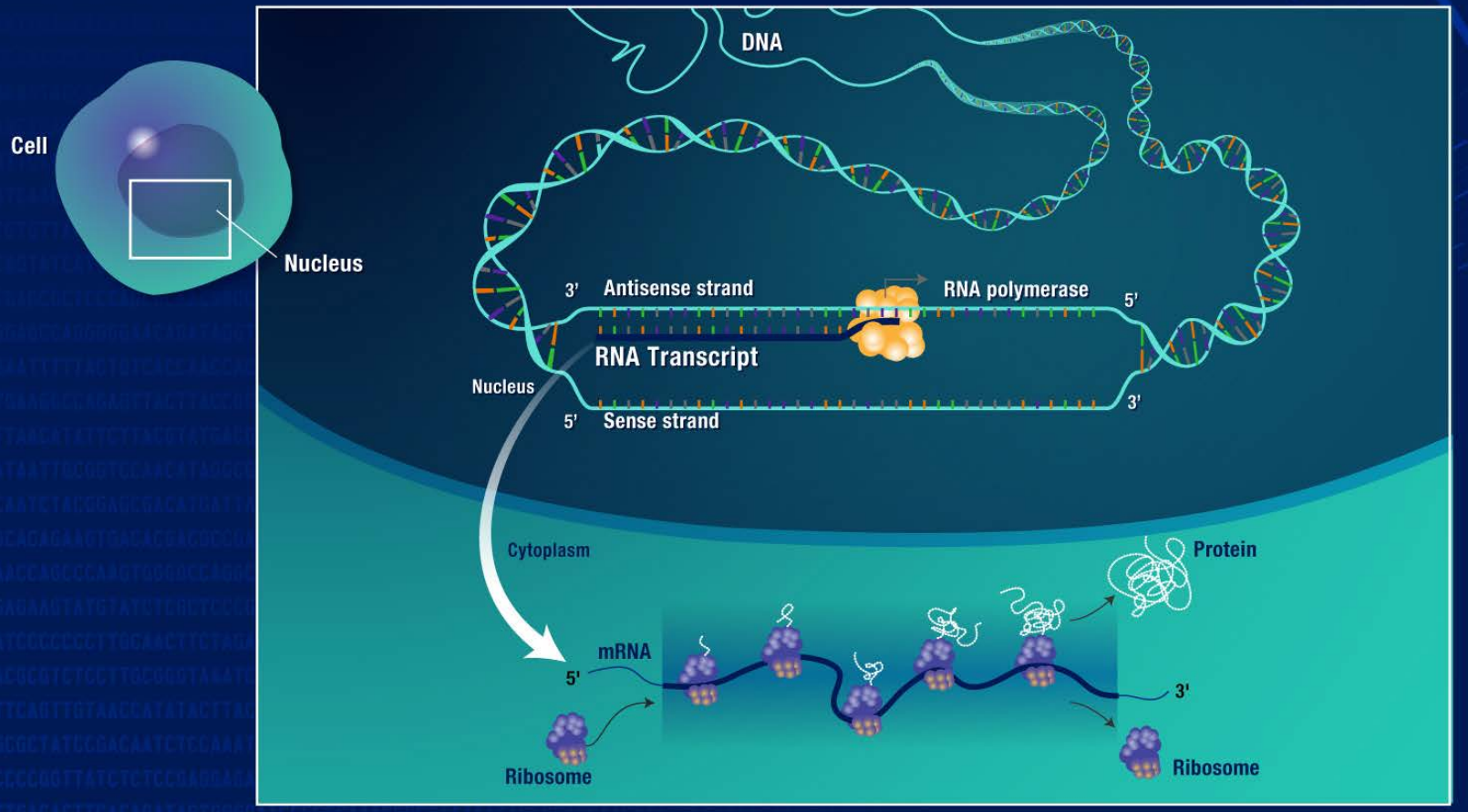
- Osimertinib, erlotinib, gefitinib, afatinib, dacomitinib
- Amivantamab, mobocertinib
- Sotorasib, adagrasib*
- Brigatinib, alectinib, lorlatinib
- Tratuzumab-deruxtecan
- Dabrafenib/trametinib
- Crizotinib, entrectinib
- Selpercaptinib, pralsetinib
- Larotrectinib, entrectinib
- Capmatinib, tepotinib

*breakthrough designation


A Brief Guide to Genomics
NHGRI FACT SHEETS
genome.gov
DNA (Deoxyribonucleic Acid)
Base Pairs
Histones
Nucleosomes
Gene
Chromosome
Cell during prophase
Cells
NIH
National Human Genome Research Institute

Transcriptome

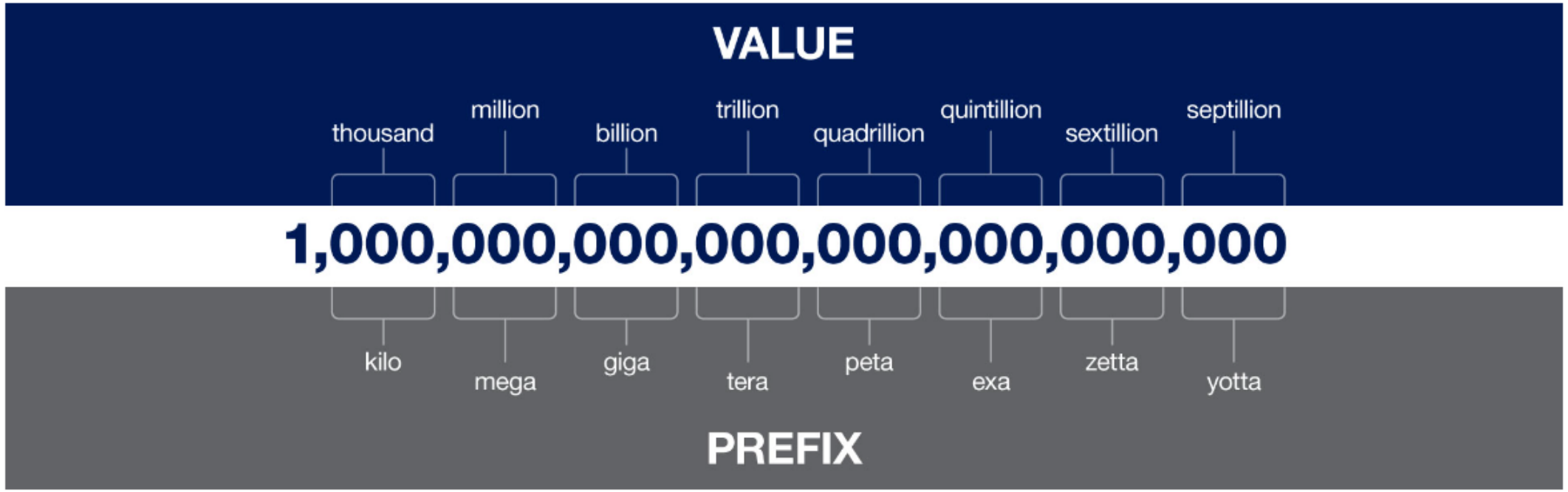
NHGRI FACT SHEETS
genome.gov



NIH National Human Genome Research Institute

Why is there a need for AI/ML in genomics?

As of 2021, 20 years have passed since the landmark completion of the draft human genome sequence. This milestone has led to the generation of an extraordinary amount of genomic data. Estimates predict that genomics research will generate between **2 and 40 exabytes** of data within the next decade.



DNA sequencing and other biological techniques will continue to increase the number and complexity of such data sets. This is why genomics researchers need AI/ML-based computational tools that can handle, extract and interpret the valuable information hidden within this large trove of data.

https://www.genome.gov/about-genomics/educational-resources/fact-sheets/artificial-intelligence-machine-learning-and-genomics