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Washington, DC
MAY 15-18

060IC - From Guidelines to Practice: Applying Genetics and Genomics in Urologic Cancer Management

Monday, May 18

Faculty

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Genetic Counseling and Testing for GU Cancer

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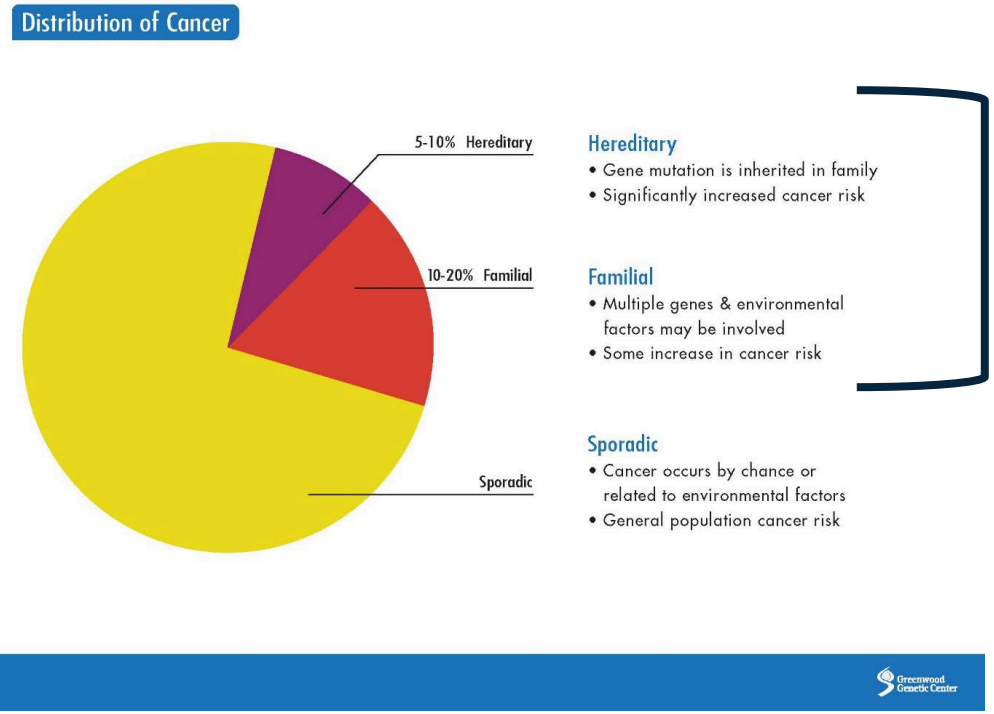
Conflicts of Interest

- None

Learning Objectives

- Describe key components of pre-test and post-test counseling in a urology setting, including risk assessment, test selection, and communication of results to patients and families.
- Interpret common genetic test results, including pathogenic/likely pathogenic variants, variants of uncertain significance (VUS), and negative results, and outline appropriate clinical management or follow-up for each.
- Evaluate the clinical utility of genetic testing in urology, including its impact on screening, treatment decisions, and cascade testing for family members.

All cancer is genetic but not all is hereditary



Why do we need to know if cancer is hereditary?

- Germline mutations that impact **treatment**
  - A ‘cause’ or ‘why’ a cancer diagnosis happened in the patient or family
- If the patient has increased cancer risk that changes **medical screening/management**
- **It’s likely** other family members need testing, increased screening, etc.

Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy

Pengfei Zhao,[#1] Li Li,[#2] Xiaoyue Jiang,[2] and Qin Li[2]

AUA Guidelines for Clinically Localized Prostate Cancer

4. Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes mutations known to be associated with aggressive prostate cancer and/or known to have im-plications for treatment.

(Expert Opinion) Germline testing in patients with clinically localized prostate cancer has several potential goals, including enhanced risk stratification, identification of genes that may guide treatment decisions, and providing information to determine the need for personal and family member cancer screening. …**Patient education, testing, and referral to a genetic counselor should be considered.** …A number of the indications for germline testing are provided in Table 4. **Importantly, patient and family history risk factors should be investigated by the clinician through careful history taking,** while pathology from biopsy or radical prostatectomy should be reviewed in the consideration of germline testing

Table 4. *Indications for Germline Testing in Patients with Clinically Localized Prostate Cancer**

Strong family history of prostate cancer	Examples: first-degree relative or multiple second-degree relatives diagnosed with Grade Group 2 or higher prostate cancer, particularly at early age (<60 years), particularly if metastatic or lethal
Strong personal or family history of related cancers	Examples: breast, colorectal, ovarian, pancreatic, upper tract urothelial carcinoma
Known family history of familial cancer risk mutation	Examples: *BRCA1, BRCA2, ATM,* Lynch-syndrome associated genes
Ashkenazi Jewish ancestry	Particularly in patients with Grade Group 2 or higher disease
Adverse tumor characteristics	Examples: High-risk disease; intermediate-risk disease with intraductal or cribriform morphology

* The Panel recognizes that this list is not exhaustive.

Eastham et al 2022 https://doi.org/10.1097/JU.0000000000002757

Genetic Counseling and Testing Defined

Genetic Counseling

- **Genetic counseling** is a specialized service that helps individuals understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.
- Genetic counselors interpret family history and test results to assess risk for inherited conditions, offering support for informed decision-making regarding testing and management.
- Key benefits include understanding personal disease risk, guidance on testing, and management strategies for conditions like cancer.
- Genetic counselors exist to support this service, but anyone can provide pre/post testing counseling

Germline Testing

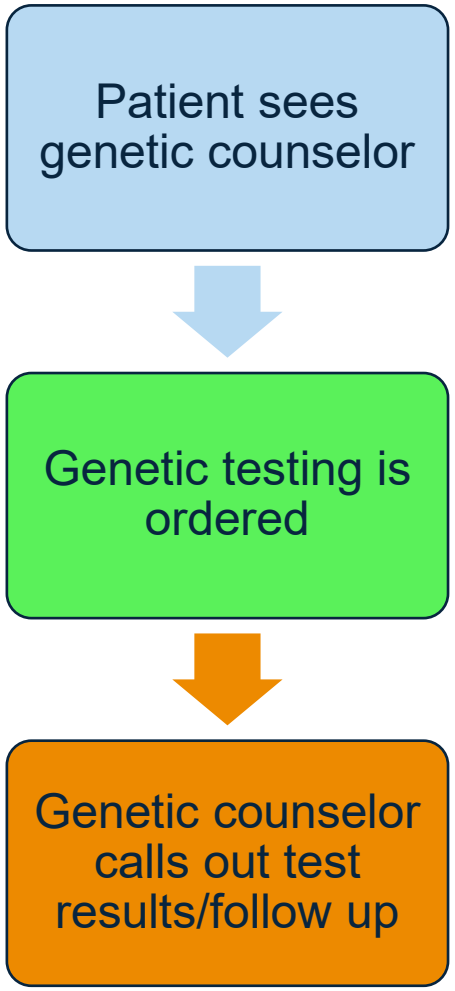
- Germline testing is a type of genetic testing that analyzes DNA from healthy cells—usually blood or saliva—to identify inherited mutations (pathogenic variants).
- It is used to determine if a person has a hereditary risk for diseases, most commonly cancers.
- Germline testing can occur without formal GC
- Results help guide treatment, risk management, and inform family members of potential risk.

Three reasons for genetics:

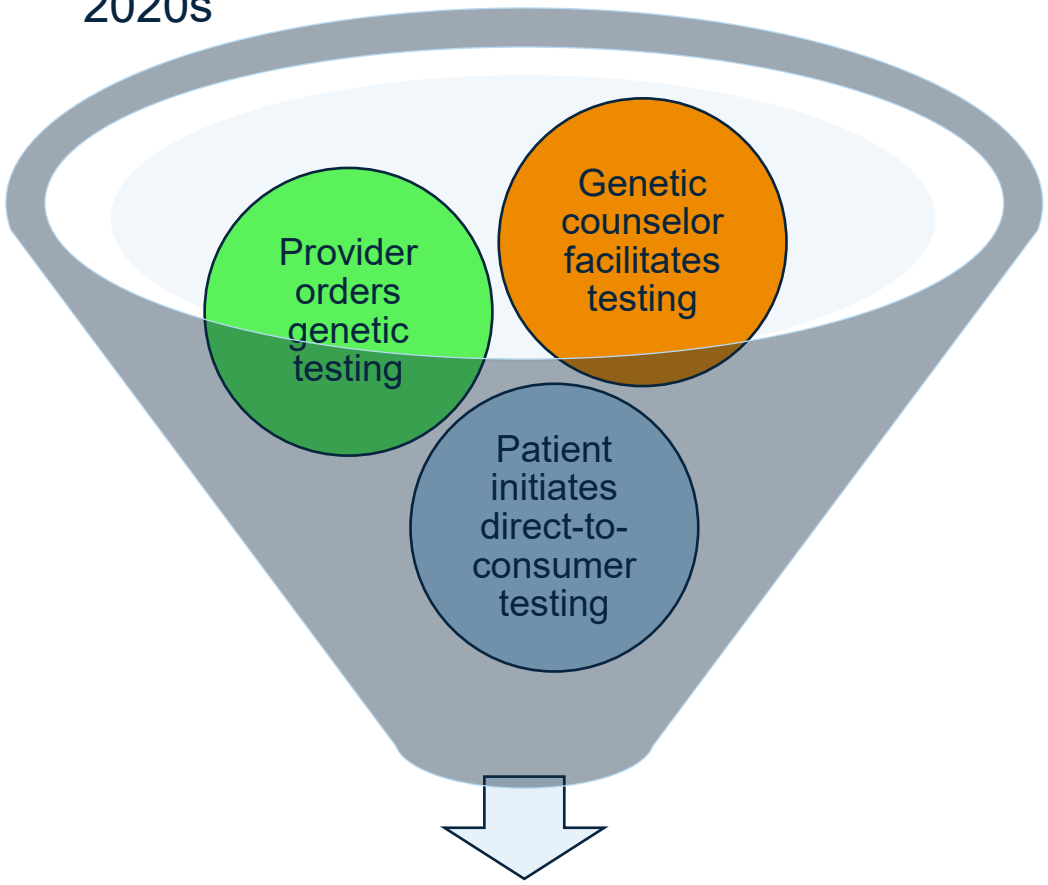
1. Treatment
2. Explanation
3. Family

Shifts in Genetics Delivery

2010s



2020s



Key components of facilitating germline testing

Credit: [Progga Jayati Biswas](#) **on LinkedIn**

Comprehensive Family History is Crucial

- Family history should occur at time of diagnosis
- Assess for:
  - Any cancers in FDRs/SDRs
  - Cancer information:
    - Type?
    - Age at Dx?
    - Bilateral?
    - Previous GT?

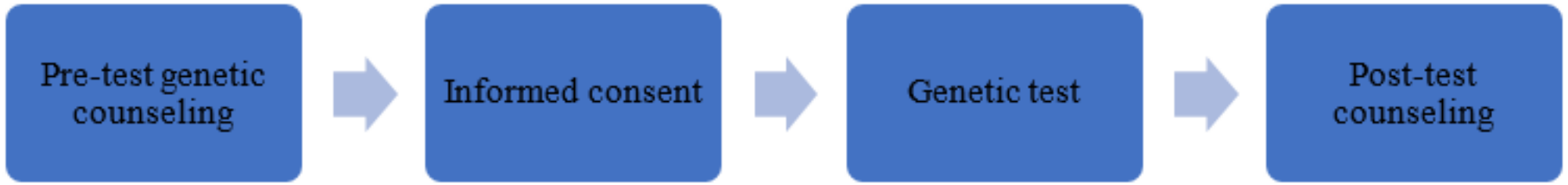
TABLE 4. Summary of all Recommendations

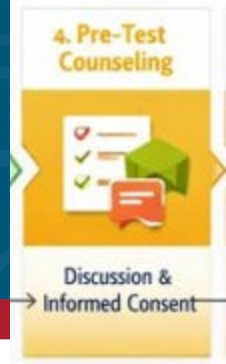
Clinical Question	Recommendation	Evidence Quality	Strength of Recommendation
Q1—Family history collection	1.1. All patients should have a family history taken and recorded	Not rated	Strong
	1.2. Patients should be asked to provide the following information as part of this family history. Patients may not have complete information, but that should not be considered an impediment to asking these questions. Only information about biologic relatives is pertinent Does the patient know of any cancers in any first-degree biological relatives: siblings, parents, children? Does the patient know of any cancers in any second-degree biological relatives (on both maternal and paternal sides): grandparents, aunts, uncles, grandchildren, nieces, nephews, half siblings? For each cancer in the family, ask for the following details: Type of primary cancer(s); age at cancer diagnosis for each primary cancer; were multiple cancers of one type involved (eg, bilateral breast cancer or multiple colon cancer primaries)? Does the patient know of any relative who has had germline genetic testing for cancer predisposition, and if so, what were the results? What is the patient's ethnicity? *Qualifying Statements:* The gender assigned at birth of biological relatives is important to the family history Where it is possible and time permits, information on third-degree relatives (eg, cousins), consanguinity, and personal and family history of colon polyps can help inform genetic testing and counseling, especially with interpretation of results	Not rated	Strong

Tung et al *J Clin Oncol* **42**, 2599-2615(2024)

Required elements of genetic risk assessment

- **Family history** including type of cancer, relation to patient, and age at diagnosis
- Appropriate **germline or somatic testing** indicated and **type/extent**
- Discussion of **limitations and outcomes** of genetic testing
-





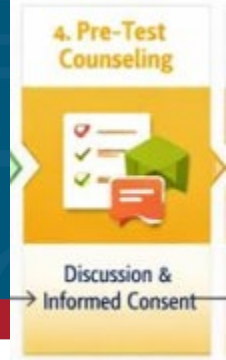
Providing Adequate Informed Consent

- ClinGen's CADRe workgroup generated expert consensus on informed consent for GT
- Core concepts:
  - What is being tested and why?
  - What will be learned?
  - How could I be impacted?
  - Limitations and next steps

- Genetic testing is always voluntary (optional)
- Why are we doing this test and what does it test for? (generally)
- What results will be returned (generally)?
- What other types of results will potentially be returned, and options for choice (such as secondary findings)?
- How if at all, will your prognosis and management (including health screening) be impacted by the results?
- The results may also impact your family in different ways (their health, emotions, or relationships), and you may want to share the result
- What are the limitations of the test, and if there is no answer, what happens next?
- To whom will the results be reported?

Figure 1. Final list of "necessary and critical" concepts for informed consent for genetic testing.

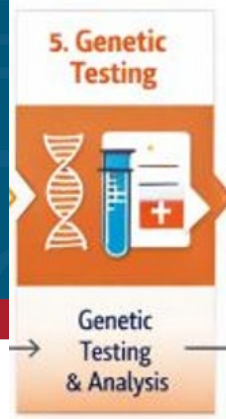
J. Pers. Med. 2021, 11(12), 1304; https://doi.org/10.3390/jpm11121304



Concerns re: Privacy, Insurance and Data

- Genetic Information Non-discrimination Act (GINA)
  - Prohibits employment and insurance discrimination based on genetic test results (i.e. GT results are not a pre-existing condition)
    - Some of this is less relevant in the wake of the ACA.
    - If anything changes, GINA will be here.
  - Does NOT apply to long-term care, life insurance, or disability insurance.
    - If your patient has cancer, that will impact their insurance rates before GT does.
  - Limits ability for payers and employers to collect genetic health information.
- Privacy Concerns (‘Golden State Killer’ question)
  - Everyone has unique genetic material that is inherently risky.
  - Clinical germline labs have significant protections for privacy that are NOT the same as genealogy or direct to consumer companies.

Genetic testing has evolved…



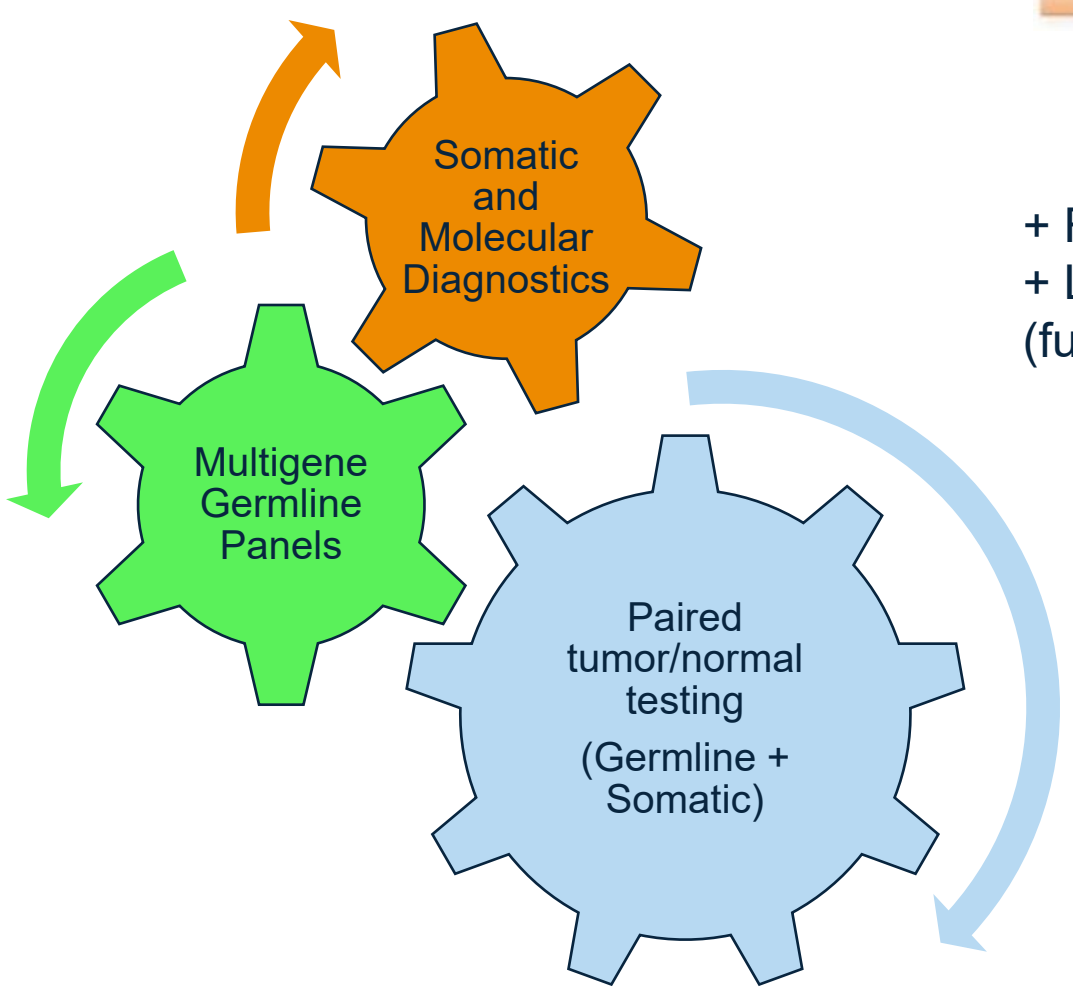
Until 2015

Most suspicious gene is tested

If insurance allows, next suspect gene tested

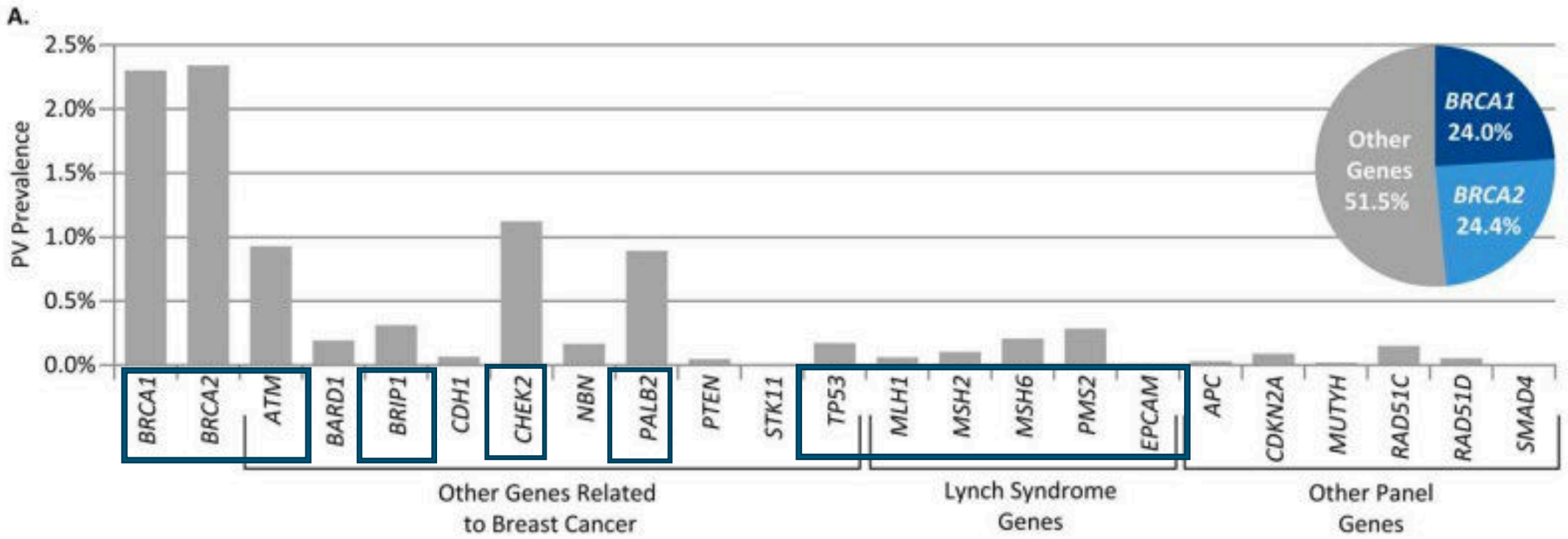
Combination of sequencing and/or deletion/duplication

2015-Present



+ RNA
+ LRS
(future)

Multigene Panel testing: Hereditary cancer and prostate risk



Buys, S. S., *Cancer*, *123*(10), 1721-1730.
Pritchard, C. C., *N Engl J Med*, *375*, 443-453.
Maxwell, K. N., *European Urology*, *81*(3), 243-250.

Quick facts on Genetic Testing

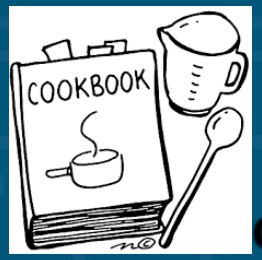
Genetic testing logistics

- Typically blood or saliva sample
- 2-4 week turn around time
- Multiple labs and testing options

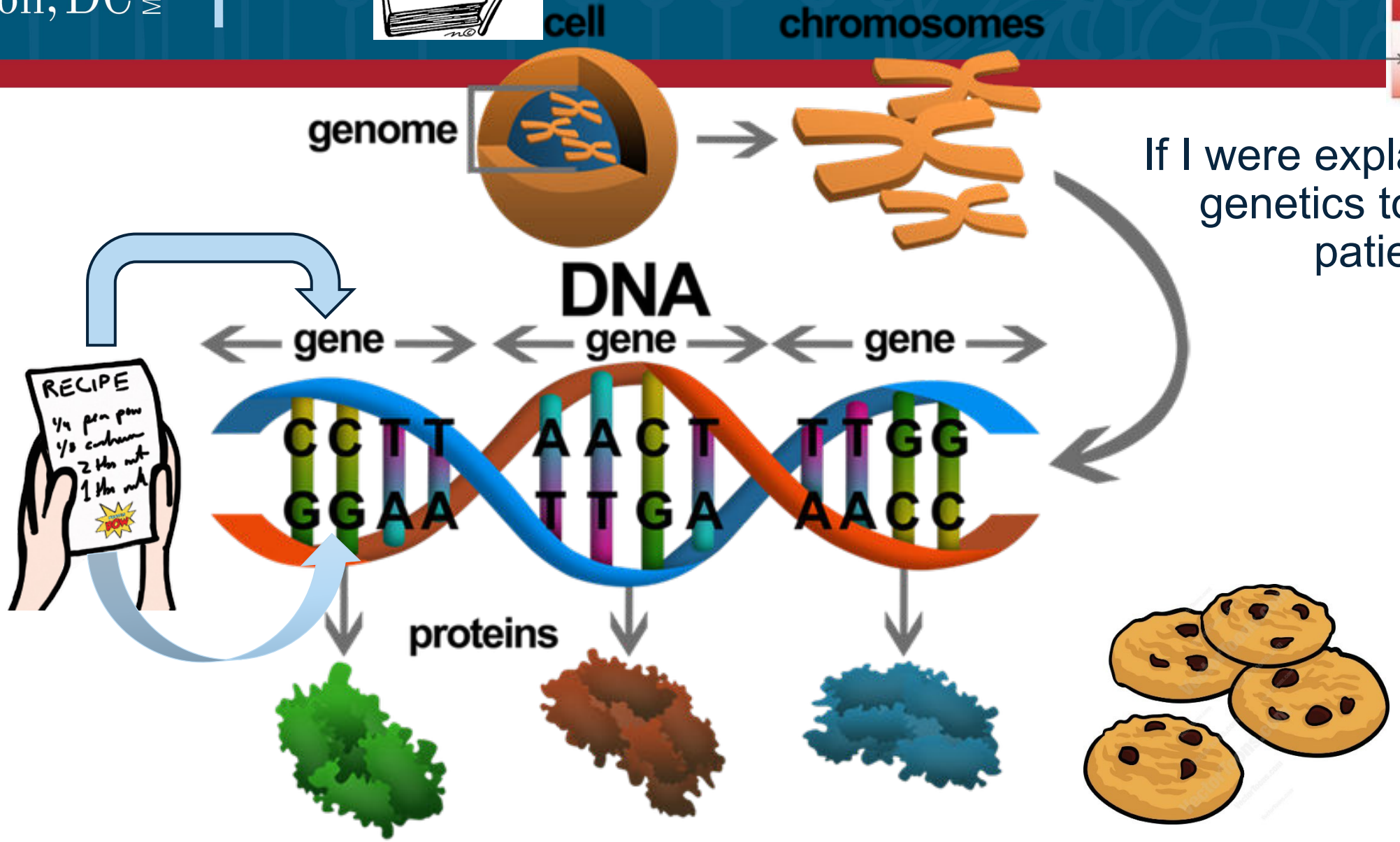
Genetic testing coverage

- Each insurance has testing criteria, most follow Medicare or NCCN guidelines
- Many laboratories (or GC) will take care of preauthorizations needed for GT
- Options for self pay or underinsured ($250), most patients pay <$100
- For family members needing testing: GINA applies

Not all labs are created equal!
Differences in: cost, family member testing, variant classification, genes included

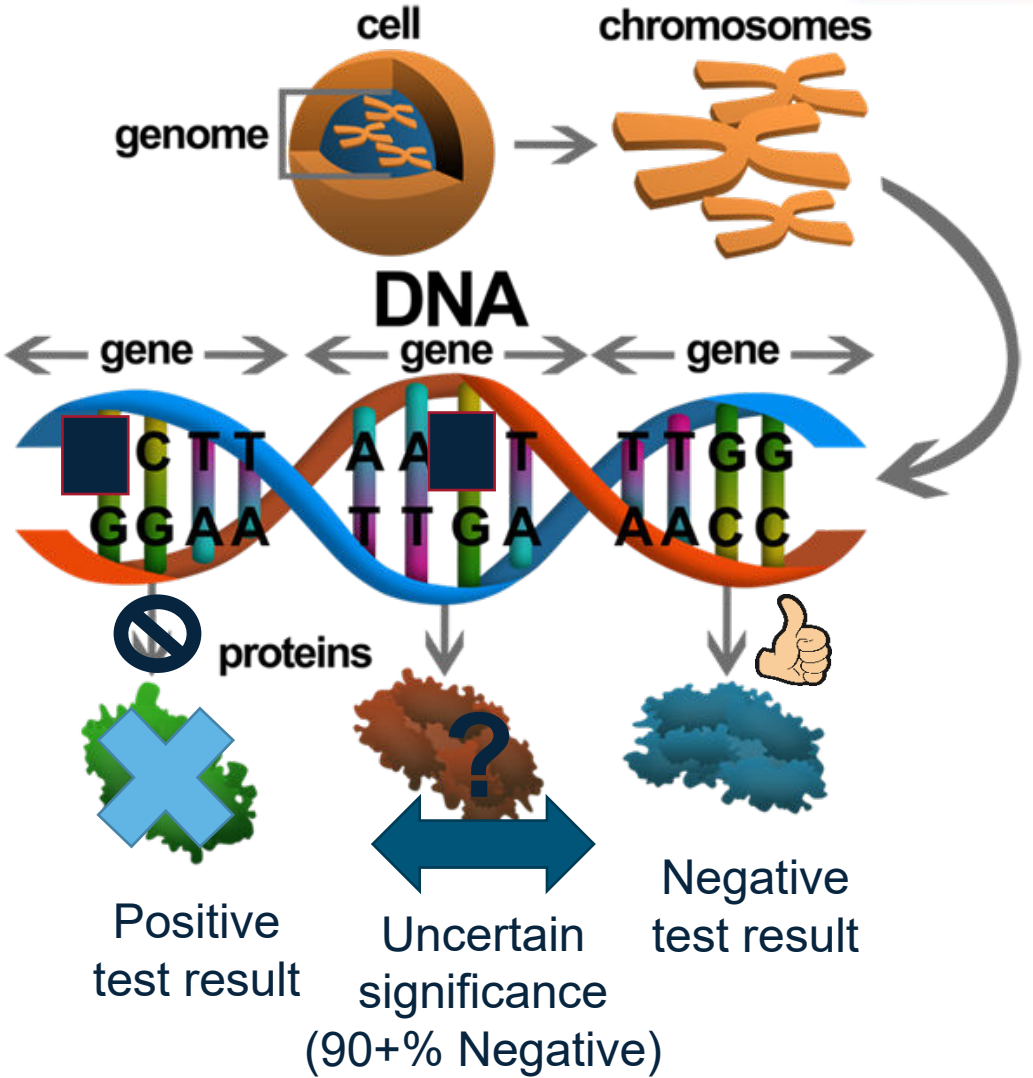


If I were explaining genetics to your patients…

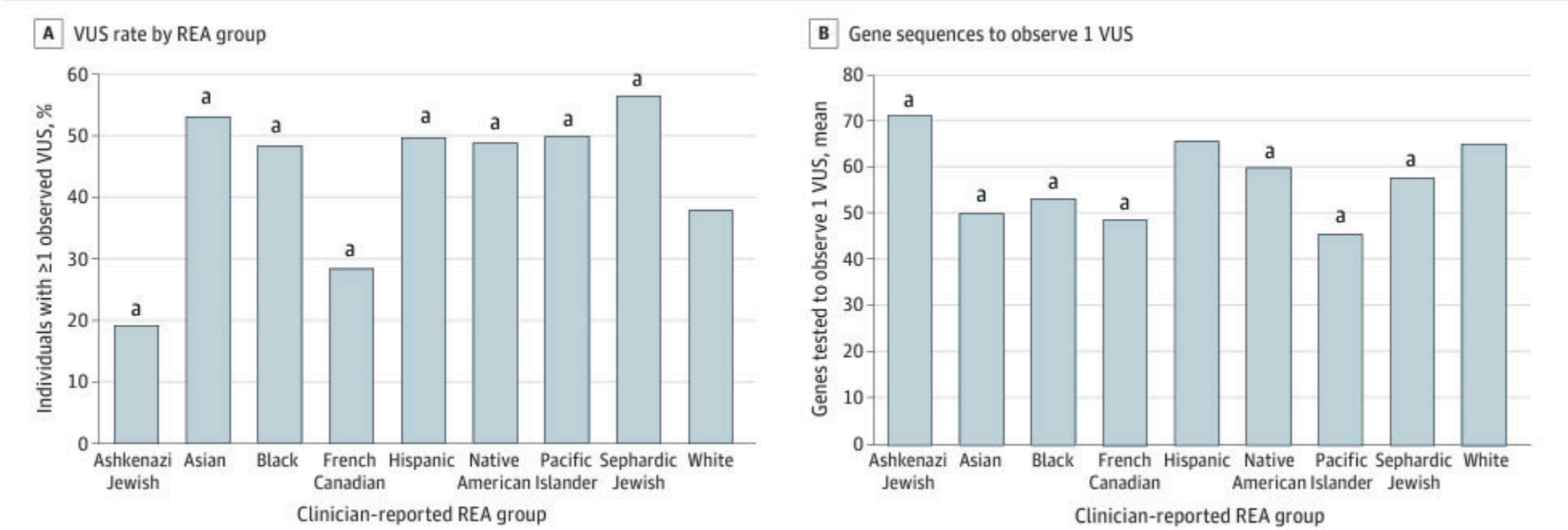


Genetic Testing Outcomes

- **Pathogenic Variant:** A change in the DNA that does not produce protein correctly, increasing cancer risk
  - i.e. positive result, mutation, deleterious mutation
- **Variant of Uncertain Significance:** A change in the DNA with unclear impact on protein
  - Typically re-classified as NOT a mutation
- **Negative:** No change in the DNA was detected that impacts health/cancer risk



VUSs are not ‘created equal’ given historical patterns of research



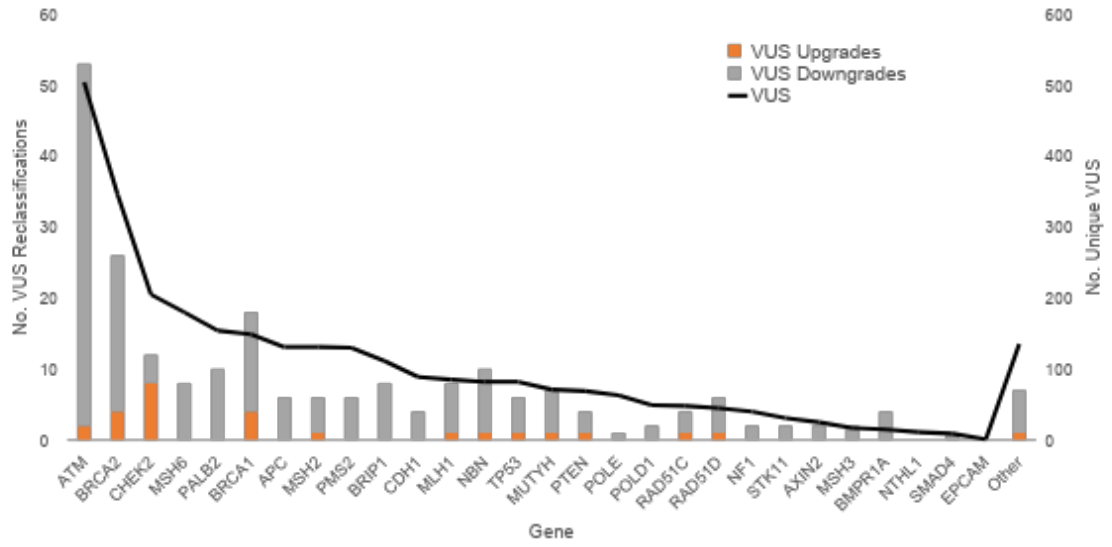
Chen E, et al. *JAMA Netw Open.* 2023;6(10):e2339571. doi:10.1001/jamanetworkopen.2023.39571

Re-classification of variants in cancer genes

Most cancer VUSs are downgraded (~90%)

	No. Unique Variants (n=3,574)		
	P/LP	VUS	Total
No. Initially detected	313	3,261	3,574
No. Reclassified (%)	7 (2.23)	240 (7.36)	247 (6.91)
Upgraded (%)	5 (71.4)	27 (11.3)	32 (12.9)
Downgraded (%)	2 (28.6)	213 (88.7)	215 (87.1)

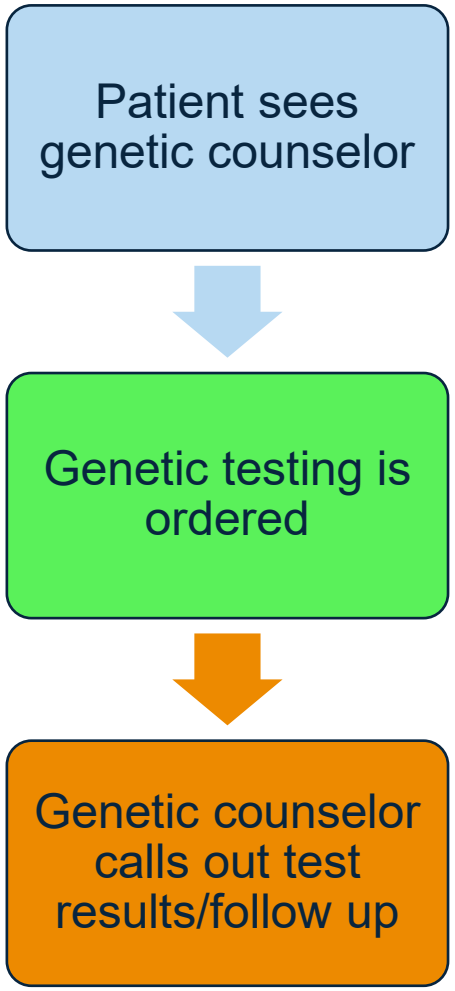
*some underwent both upgrade and downgrade; Variant reclassifications were defined as downgrades if the variant was reclassified from P/LP to VUS, P to LP, or from VUS to B/LB, and upgrades if the converse happened.



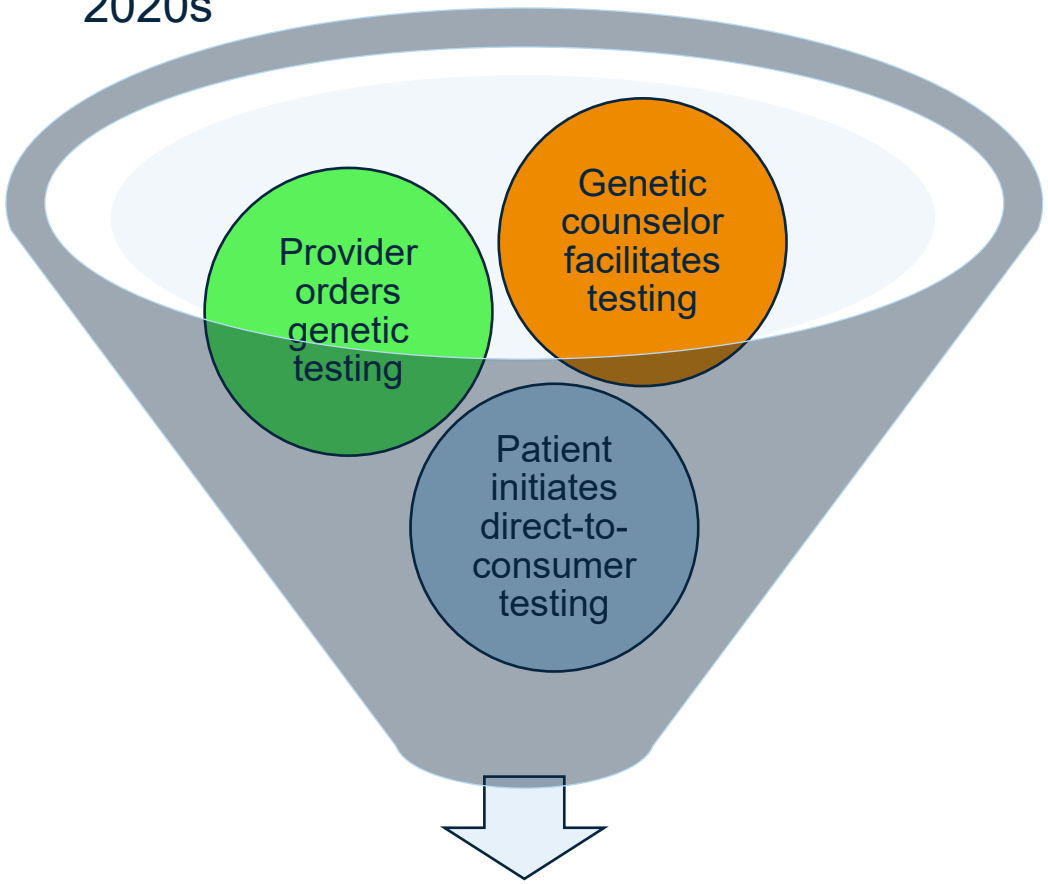
Makhnoon et al 2022 *Cancer Medicine* https://doi.org/10.1002/cam4.5202Digital Object Identifier (DOI)

Shifts in Genetics Delivery

2010s



2020s



Genetic testing results are disclosed

Incorporating video education into GU oncology GT

Paper	Location (n)	Who discusses GT	Who orders GT	Outcome
Hamilton	MSK (n=1,203)	Oncologist/Video	Oncology support	90% uptake High acceptability 10% PV rate
Kwon	UCSF (n=731)	Oncologist/Video	Genetic support	83% uptake 10% cost savings Higher odds of timely completion
Rana	Multi-site GC vs video (n=662)	Video or Genetic Team	Genetic support	No differences in uptake or genetic testing knowledge DFCI switched to 100% video

Videos ranged from 8-11 minutes (when described) and most PV rates >10%

Hamilton, J. G (2021). *Genetics in Medicine*, *23*(11), 2105-2113.
Kwon, D. (2023). *JCO Oncology Practice*, *19*(5), e773-e783.
Rana, (2023). *JCO Oncology Practice*, *19*(11), 1069-1079.

Diverse range of models used in GU Germline Testing

- Post-referral, when patients given video versus genetic counseling choice, 71% selected video (Russo)
- Patient-driven internet-based programs recruited 816 patients with an 86% genetic testing completion rate (Cheng)
- Clinician-led genetic counseling resulted in 98% satisfaction rate (n=265) with a 74% genetic testing uptake rate (Abusamra)

Though we are shifting to new models, we continue to see disparities in germline testing uptake that must be addressed

Russo, J., (2021). *JCO Precision Oncology*, *5*, 1377-1386.
Cheng, H. H (2023) *JCO Precision Oncology*, *7*, e2200104.
Abusamra, S. M (2022). *Urology*, *208*(5), 1007-1017.

Summary

- Germline testing is an essential part of cancer workup in GU space
- Testing should include family history and risk assessment
- Administration of germline testing can occur with genetic providers, urologists, or in partnership
- Patients are comfortable with multiple types of genetics service delivery

Genetic evaluation of urothelial cancer of the bladder and upper tract

Jonathan Coleman, MD

Memorial Sloan Kettering Cancer Center

May 11, 2026

Memorial Sloan Kettering
Cancer Center

Disclosures

- No Relevant Financial Relationships

- Investigator for clinical trials in UTUC
  - Photodynamic therapy for UTUC (ENLIGHTED)
  - Adstiladrin for UTUC (Ferring)

- Research Funding
  - Thompson Foundation Grant
  - NIH/NCI
  - DOD

Overview and Objectives

- Understand indications for genetic testing
- Differentiate germline vs somatic alterations
- Integrate results into clinical care

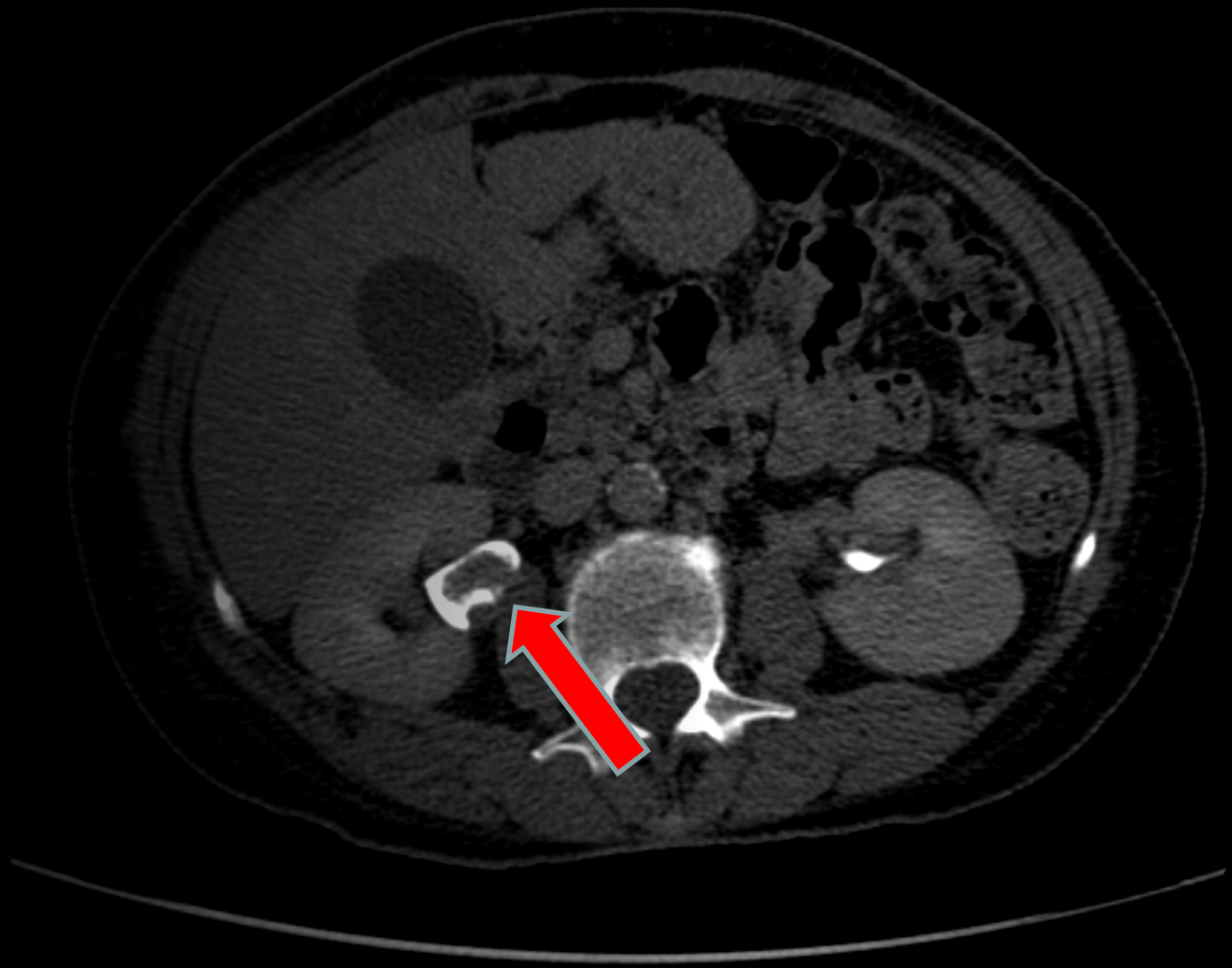
Case: Hematuria Evaluation

- 71 yo woman, microhematuria
- PMH: lung cancer (NED x 5 yrs)
- PSH: VATS pneumonectomy
- Social Hx: 35 pack year, quit 15 yrs
- Family History: Poor historian, No known cancers

- Exam: Unremarkable
- GFR = 63

CT scan

No Lung or other masses



Course: Diagnostic Endoscopy

Diagnostic Ureteroscopy:

-Ureteroscopy and Biopsy, Laser Fulguration

- Pathology: High grade TCC, Solitary lesion

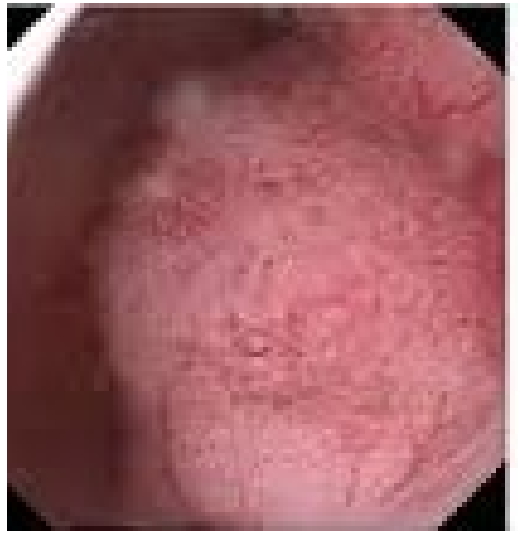
Next?

Nephroureterectomy

Neoadjuvant Therapy

Endoscopic Resection

Further Testing



Path Addendum: MMR Immunohistochemistry

MLH1: Staining present in tumor

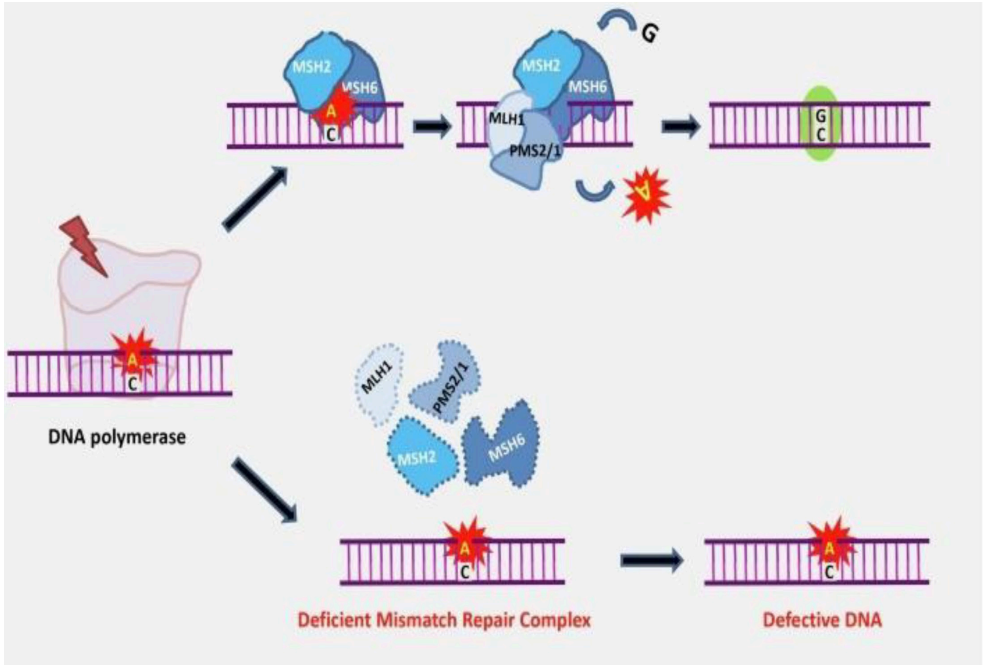
MSH2: Staining absent in tumor

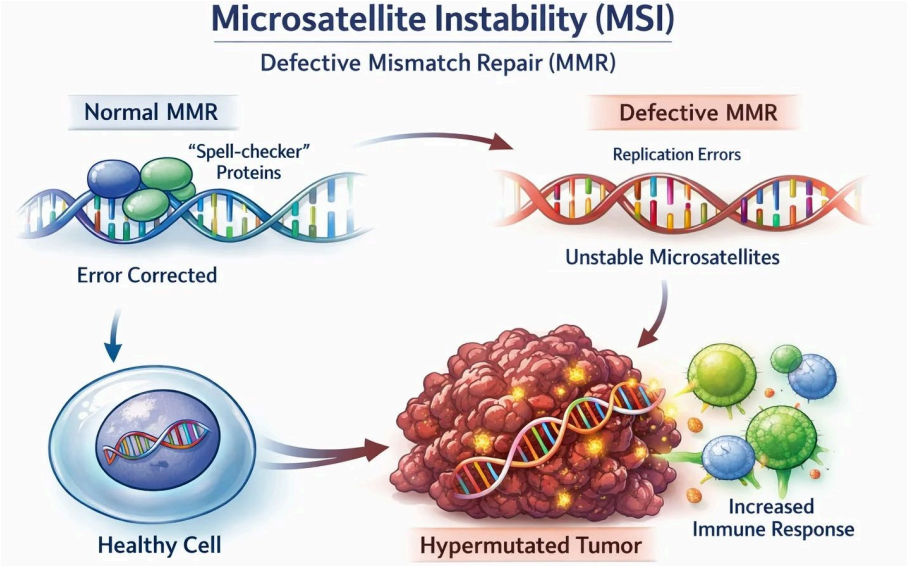
MSH6: Staining focally present in tumor

PMS2: Staining present in tumor

What is MMR Testing?

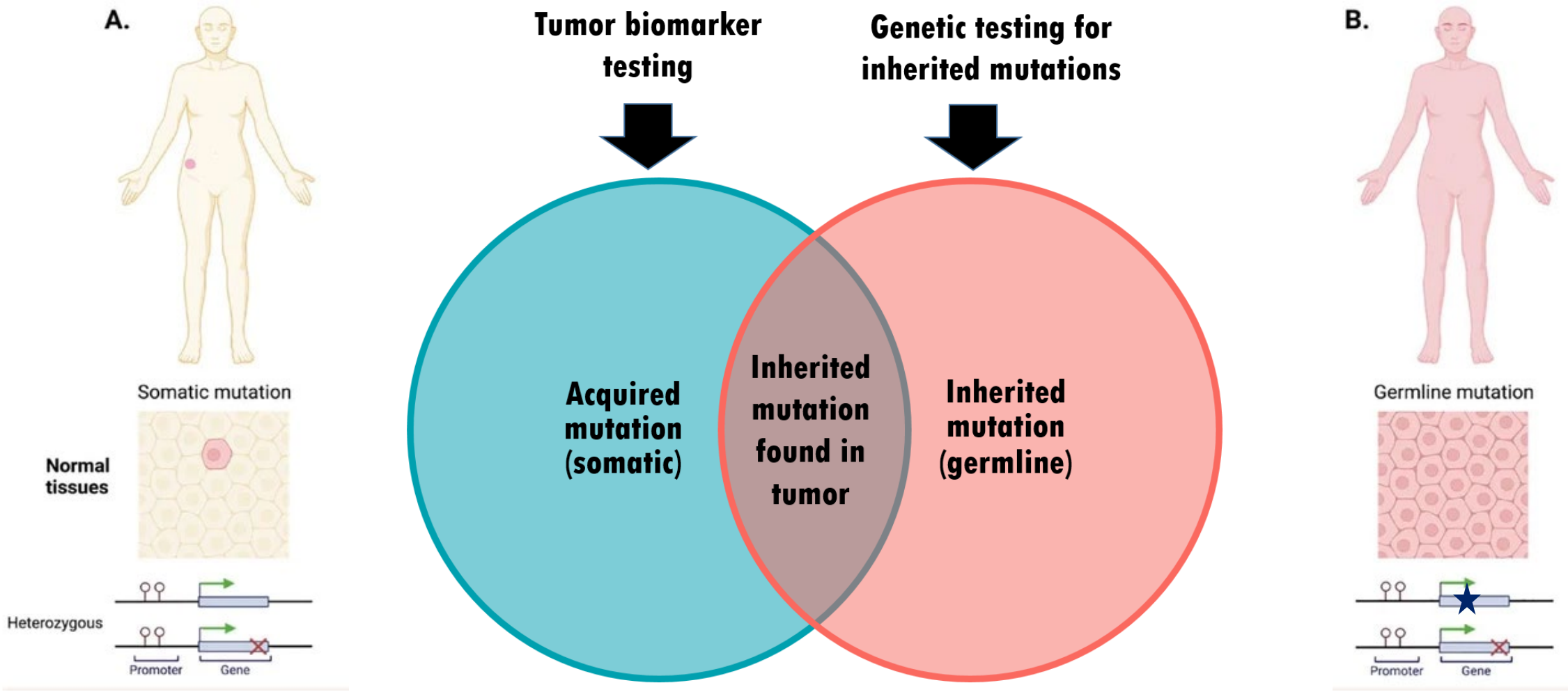
- MMR = DNA Mismatch Repair
  - MLH1, MSH2, MSH6, PMS2/1, EPCAM
- Loss of function or deficiency results in failure to repair DNA mismatches and increases risk of mutations and Microsatellite Instability (MSI)
- Gene function can be checked with Immunohistochemistry (protein) or PCR (MSI). These tests are complementary
- Germline dMMR = Lynch Syndrome
- MMR status testing is not genetic testing





Moon et al. Int. J. Mol. Sci. 2021

Biomarker Testing vs Genetic Testing



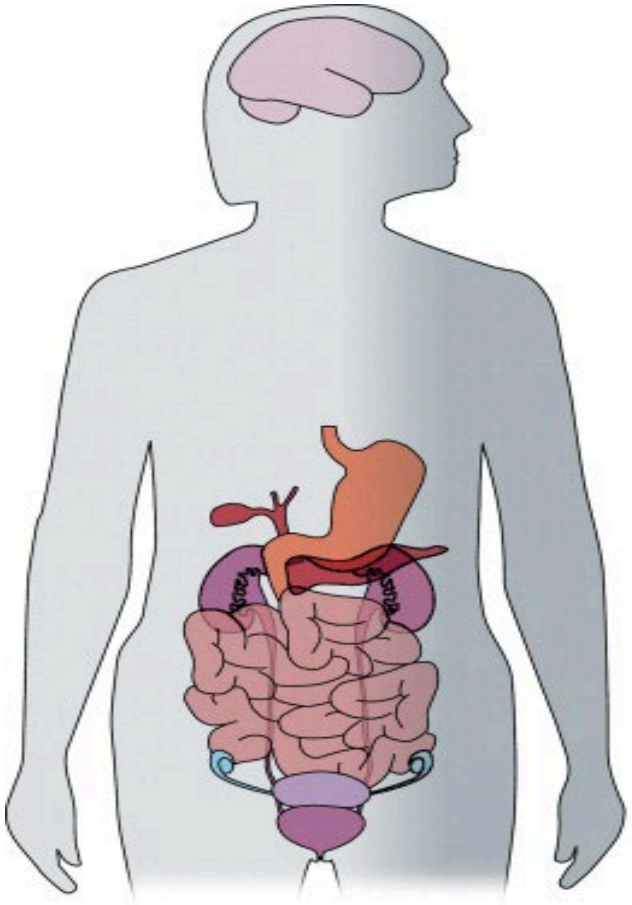
Geissler, et al, Therapeutic Advances in Medical Oncology (2024)

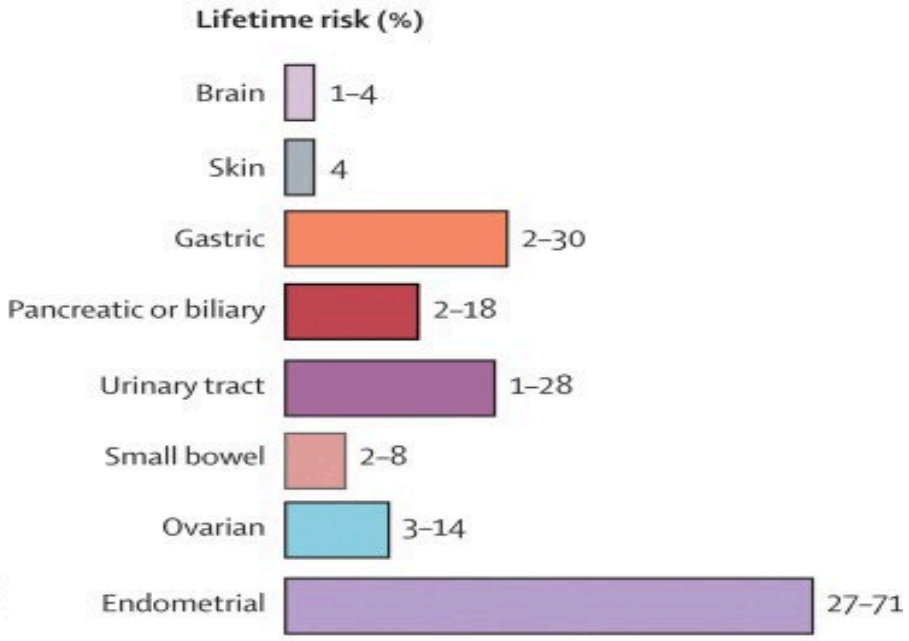
Risk Factors: Lynch Syndrome

- **Lynch syndrome (LS, HNPCC): autosomal dominant, multi-organ cancer syndrome caused by a germline mutation in mismatch repair (MMR) genes**

- **Characterized by:**
  - **Malignancy at young age (<50 yo)**
  - **High risk of colorectal (25 – 70%) and endometrial cancer (30 – 70%)**
  - **Increased risk of developing extra-colonic cancers**
  - **Ovarian, small bowel and biliary tract, sebaceous gland tumors, and UT urothelial cell carcinomas (22 fold increase)**

Lynch Syndrome





Prostate Cancer

1 in 279 people carry LS

80% of affected individuals will develop cancer

3.5 Million patients fall within LS spectrum cancers each year

<u>3 – 2 – 1 rule:</u>

3+ relatives with LS tumors
2+ generations affected
1+ first degree relative
1+ with LS cancer < 50 yo

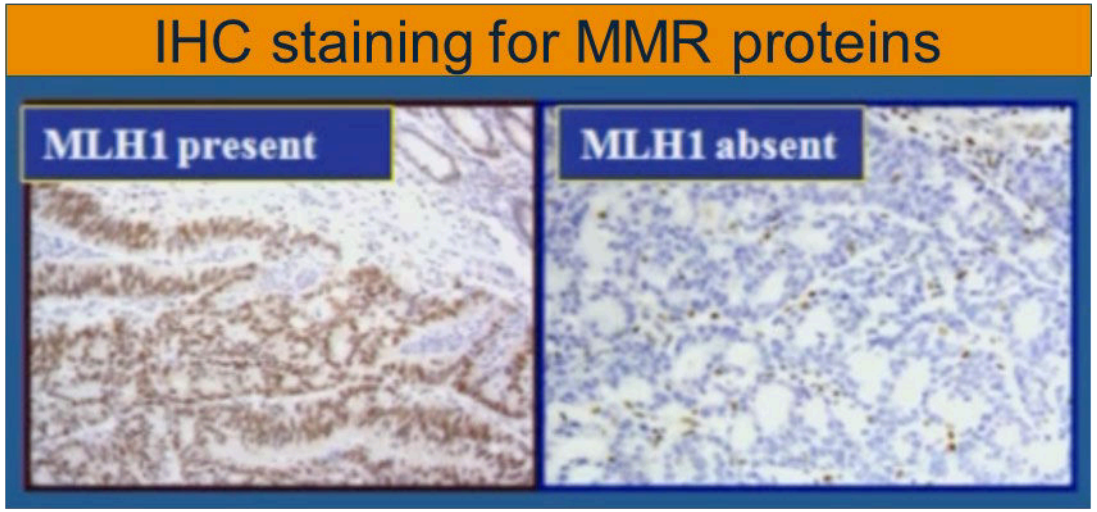
Koornstra et al, Lancet (2009)

Memorial Sloan Kettering Cancer Center

Lynch Syndrome: Universal Testing

AUA/SUO Guideline in Non-Metastatic UTUC (2023)

5. **Universal histologic testing of UTUC** with additional studies, such as immunohistochemical (IHC) or microsatellite instability (MSI), should be performed to identify patients with high probability of Lynch-related cancers whom clinicians should refer for genetic counseling and germline testing. (Strong Recommendation; Evidence Level: Grade B)



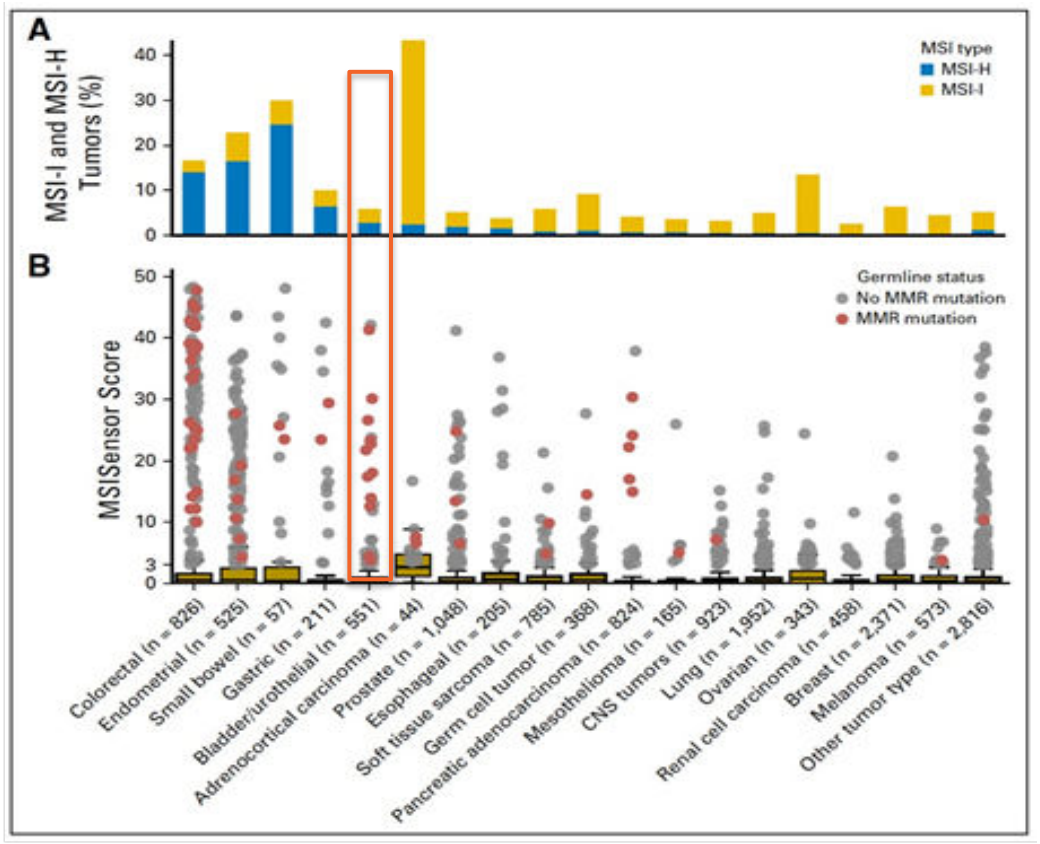
- MLH1, MSH2, MSH6, PMS2
- Loss of protein expression is indicative of dMMR

IHC Testing is Not Germline Testing and will miss 20% of Lynch Patients
Therefore, germline testing is also supported with appropriate counseling

Germline genetics of urothelial carcinoma

High MSI in UC is associated with Lynch Syndrome

If BCa or UTUC is MSI-High, what is the probability of Lynch Syndrome?



Latham A. et al., *JCO* 2018

TABLE 2. Prevalence of Lynch Syndrome by Tumor Type and MSI Status

Tumor Type	Total Count	MSI-H/I	% MSI-H/I Lynch	95% CI
Colorectal	826	137	19 (26/137)	12.8 to 26.6
Endometrial	525	119	5.9 (7/119)	2.4 to 11.7
Small bowel	57	17	11.8 (2/17)	1.5 to 36.4
Gastric	211	13	15.4 (2/13)	1.9 to 45.5
Esophageal	205	16	0 (0/16)	0.0 to 20.6
Bladder/urothelial	551	32	37.5 (12/32)	21.1 to 56.3
Adrenocortical	44	19	10.5 (2/19)	1.3 to 33.1
Prostate	1,048	54	5.6 (3/54)	1.2 to 15.4
Germ cell	368	33	3 (1/33)	0.1 to 15.8
Soft tissue sarcoma	785	45	4.4 (2/45)	0.5 to 15.1
Pancreatic	824	34	14.7 (5/34)	5.0 to 31.1
Mesothelioma	165	6	1.7 (1/6)	0.4 to 64.1
CNS tumors	923	30	3.3 (1/30)	0.1 to 17.2
Ovarian	343	46	0 (0/46)	0.0 to 7.7
Lung	1,952	94	0 (0/94)	0.0 to 3.8
Renal	458	11	0 (0/11)	0.0 to 28.5
Breast	2,371	150	0 (0/150)	0.0 to 2.4
Melanoma	573	25	4 (1/25)	0.1 to 20.4
Other tumor type*	2,816	144	0 (1/144)*	0.0 to 3.8

Germline genetics of urothelial carcinoma

Universal screening for Lynch in UTUC?

Universal Point of Care Testing for Lynch Syndrome in Patients with Upper Tract Urothelial Carcinoma

Michael J. Metcalfe, Firas G. Petros, Priya Rao, Maureen E. Mork, Lianchun Xiao, Russell R. Broaddus and Surena F. Matin*

115 consecutive UTUC cases without known history of Lynch syndrome

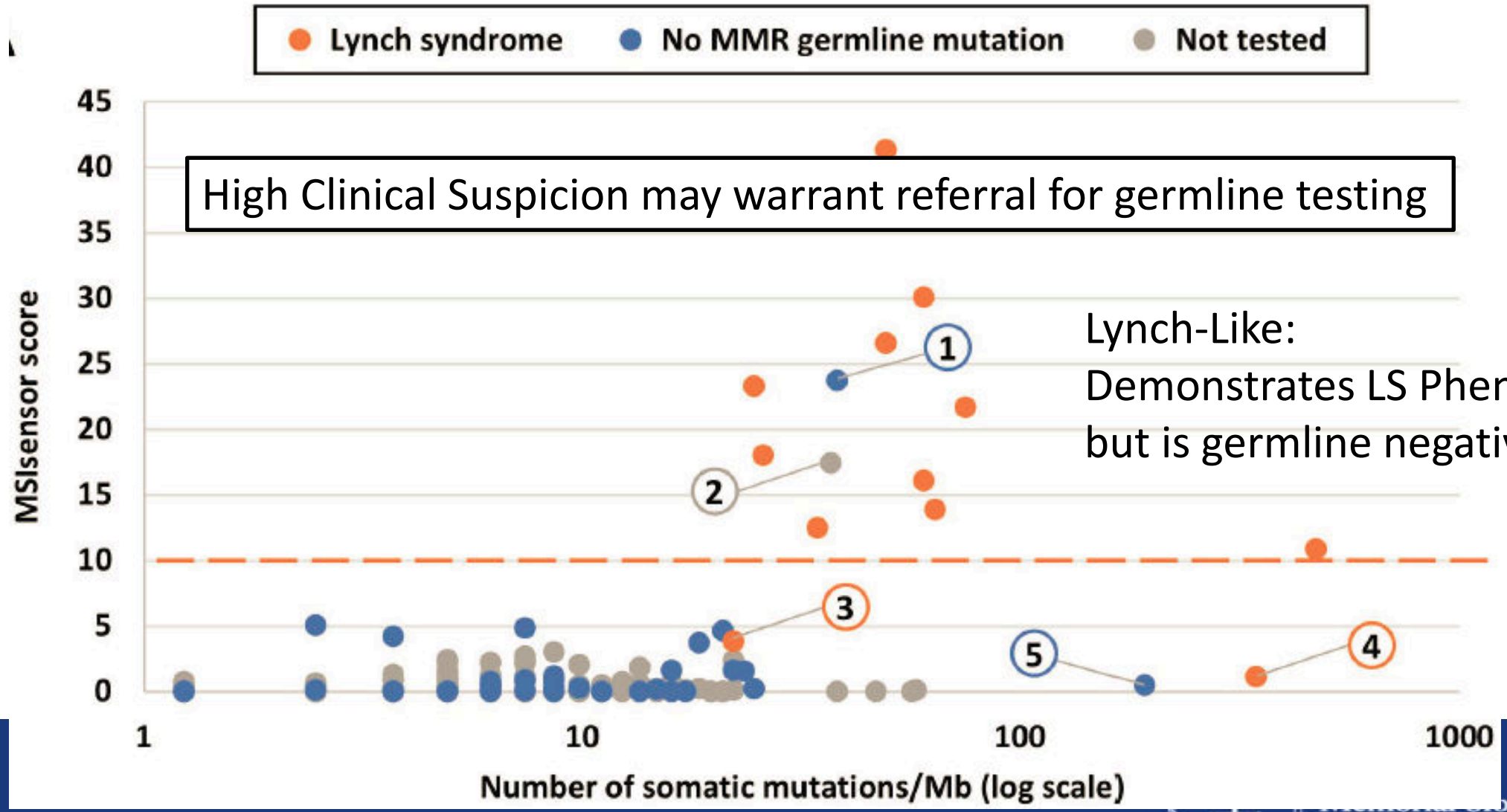
Screened for MSI, deficient MMR on IHC or meeting Amsterdam criteria

13.9% met any criteria, 5.2% were confirmed to have Lynch syndrome

	Cases in US/Year	MSI-High	Lynch Syndrome
Colorectal	150,000	15%	3%
Uterine	66,000	30%	2-5%
Upper tract UC	4-10,000	6-10%	5%

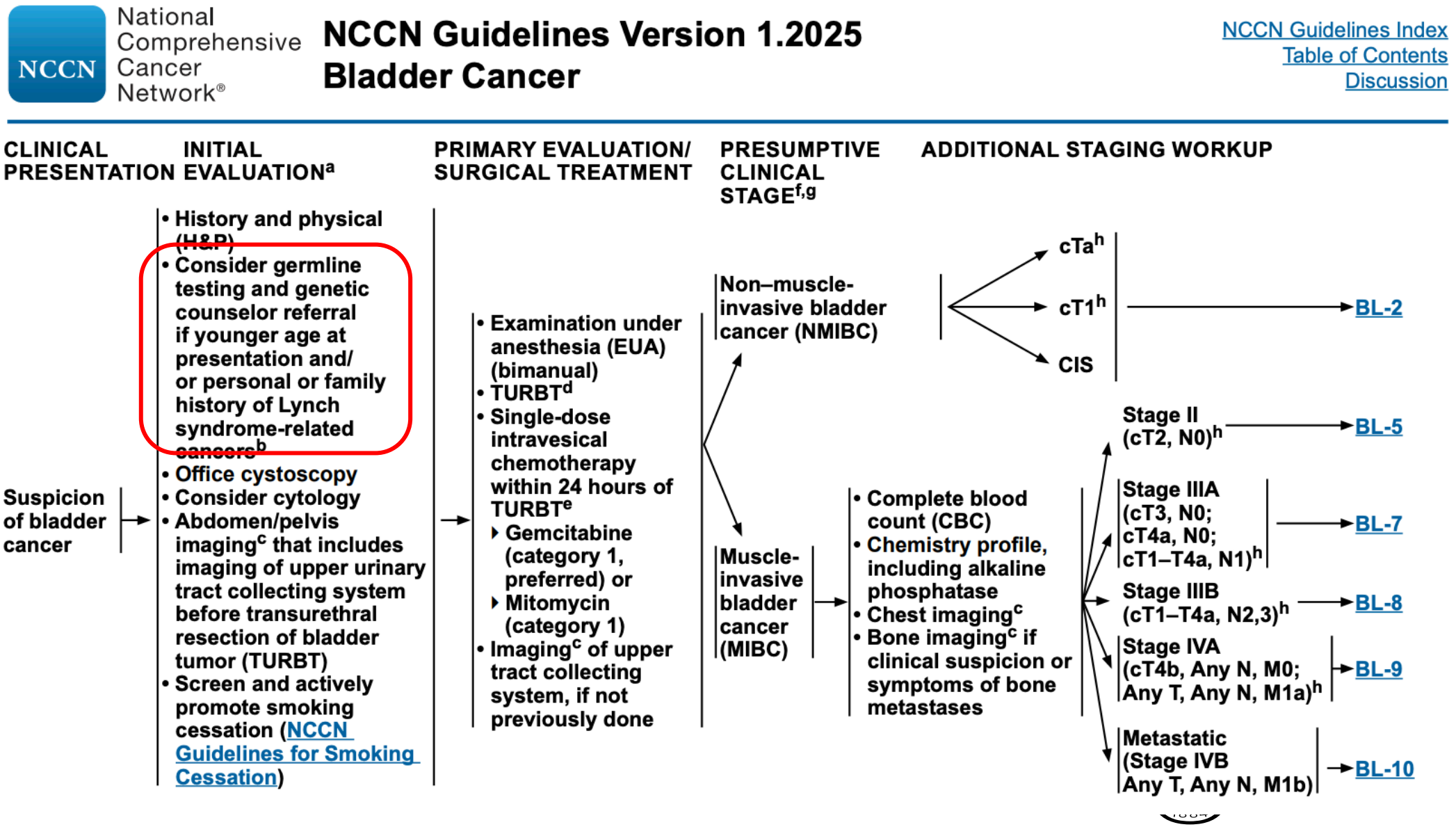
Metcalfe et al., *Journal of Urology,* 2018

Microsatellite Instability (MSI-H)

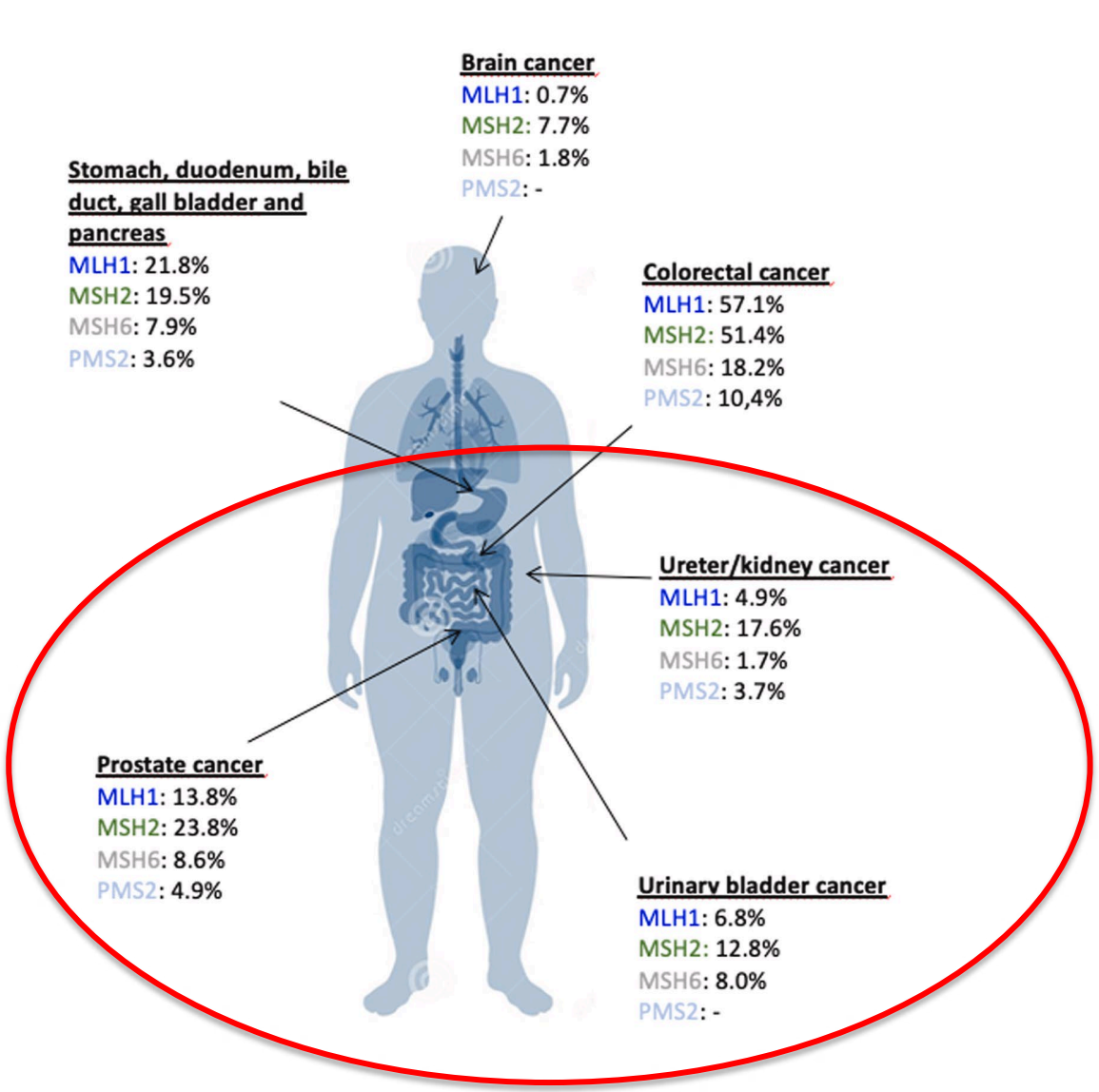


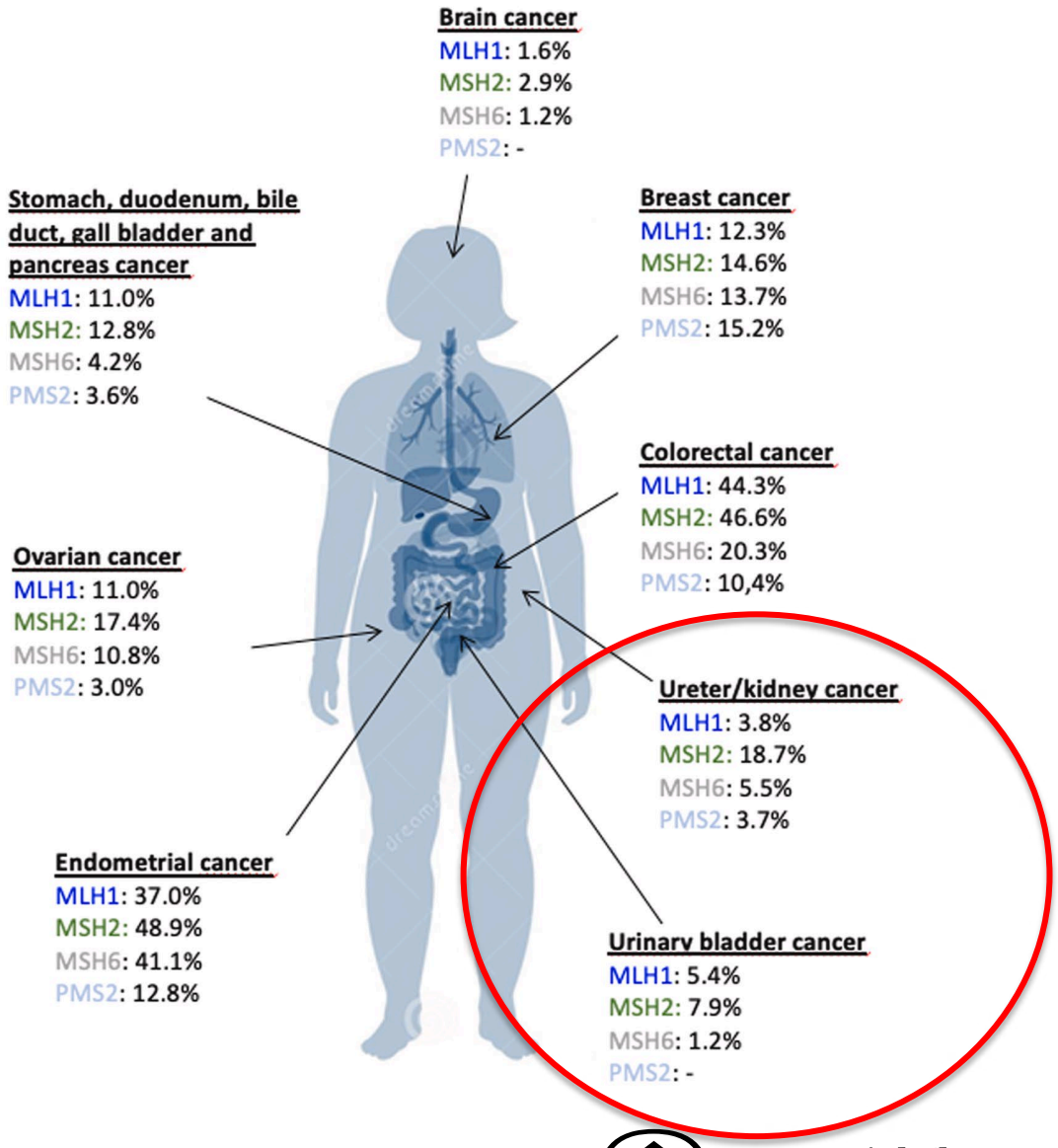
Audenet et al (Clin Cancer Res 2018)

Germline genetics of urothelial carcinoma



Screening Lynch Syndrome Patients: Lifetime Risks





Llach, et al. (2022)

Germline genetics of urothelial carcinoma

Urothelial cancer screening in Lynch syndrome

There is no clear evidence to support surveillance for urothelial cancers in LS.

Surveillance may be considered in selected individuals such as those with a family history of urothelial cancer.

Surveillance options may include annual urinalysis starting at age 30–35 y. However, there is insufficient evidence to recommend a particular surveillance strategy.

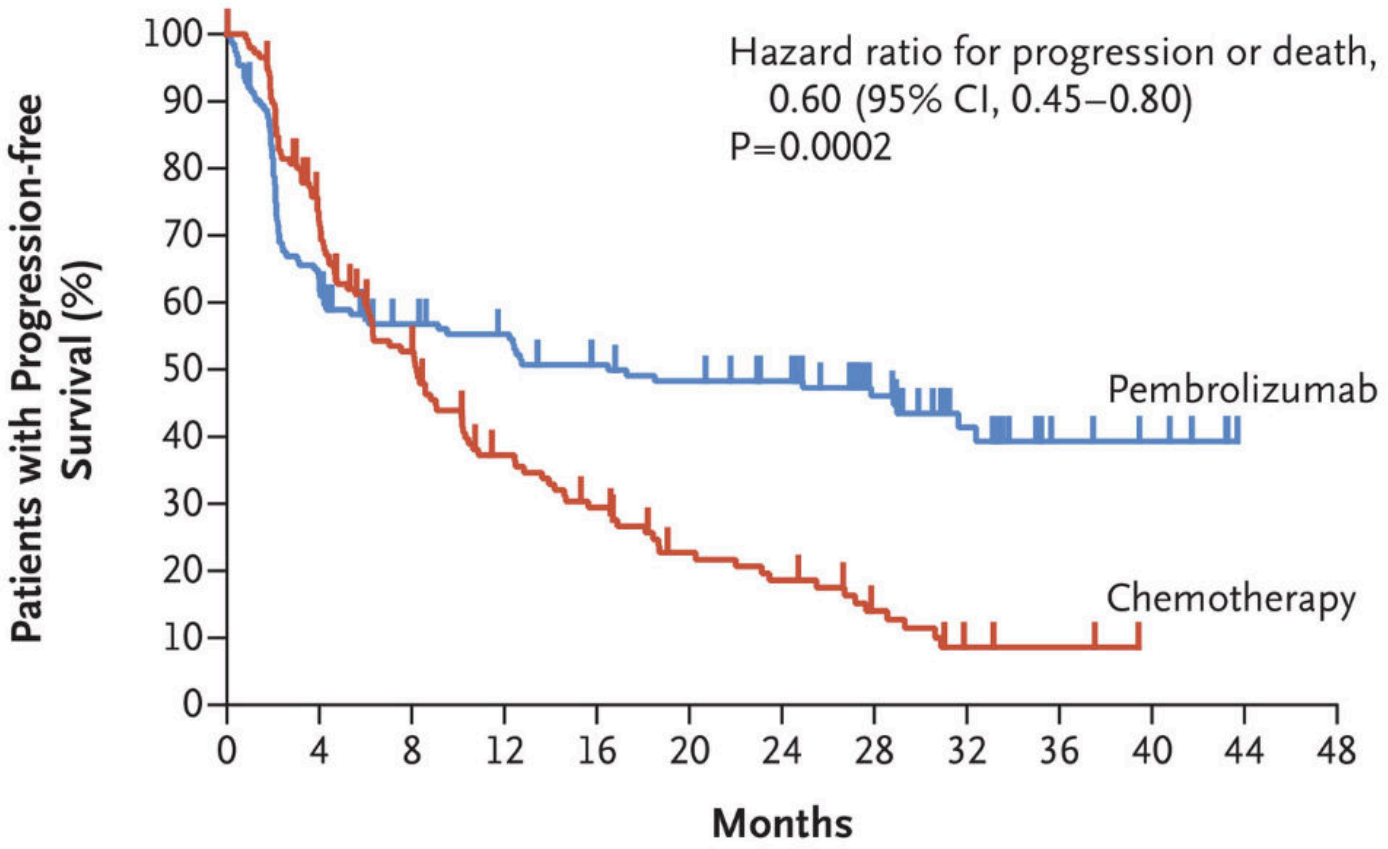
NCCN Guidelines Version 2.2023 Lynch Syndrome

Treatment for Lynch Related Cancers

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

The NEW ENGLAND JOURNAL of MEDICINE

Authors: Thierry André, M.D., Kai-Keen Shiu, F.R.C.P., Ph.D., Tae Won Kim, M.D., Ph.D., Benny Vittrup Jensen, M.D., Lars Henrik Jensen, M.D., Ph.D., Cornelis Punt, M.D., Ph.D., Denis Smith, M.D., +14, for the KEYNOTE-177



No. at Risk

Pembrolizumab	153	96	77	72	64	60	55	37	20	7	5	0	0
Chemotherapy	154	100	68	43	33	22	18	11	4	3	0	0	0

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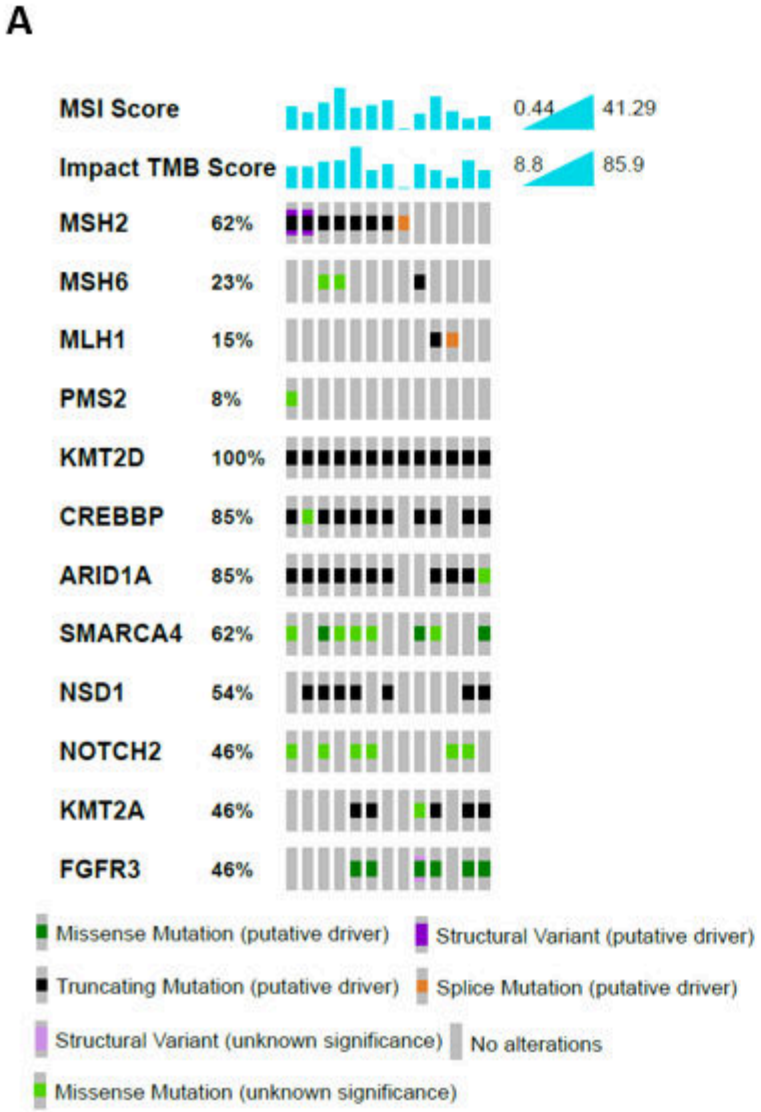
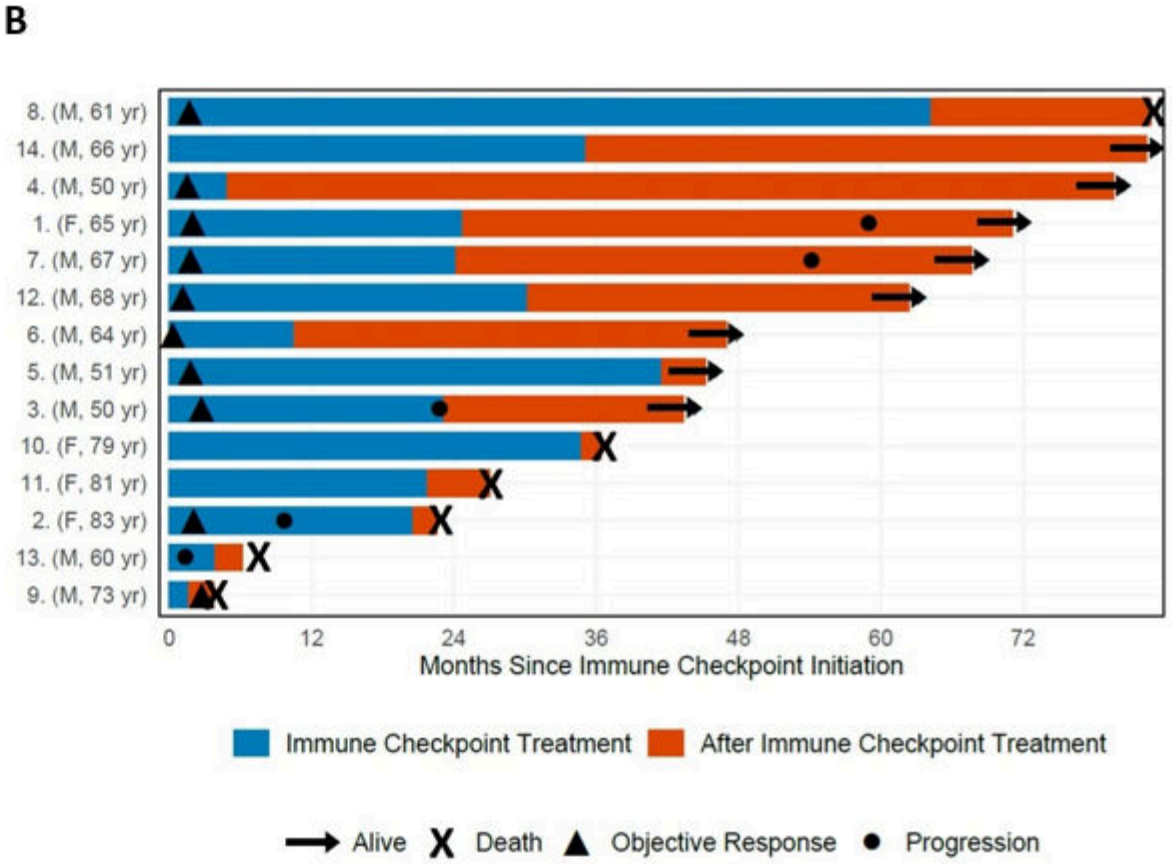
Checkpoint Inhibitors for Lynch Syndrome UTUC





Doudt et al, (2024)

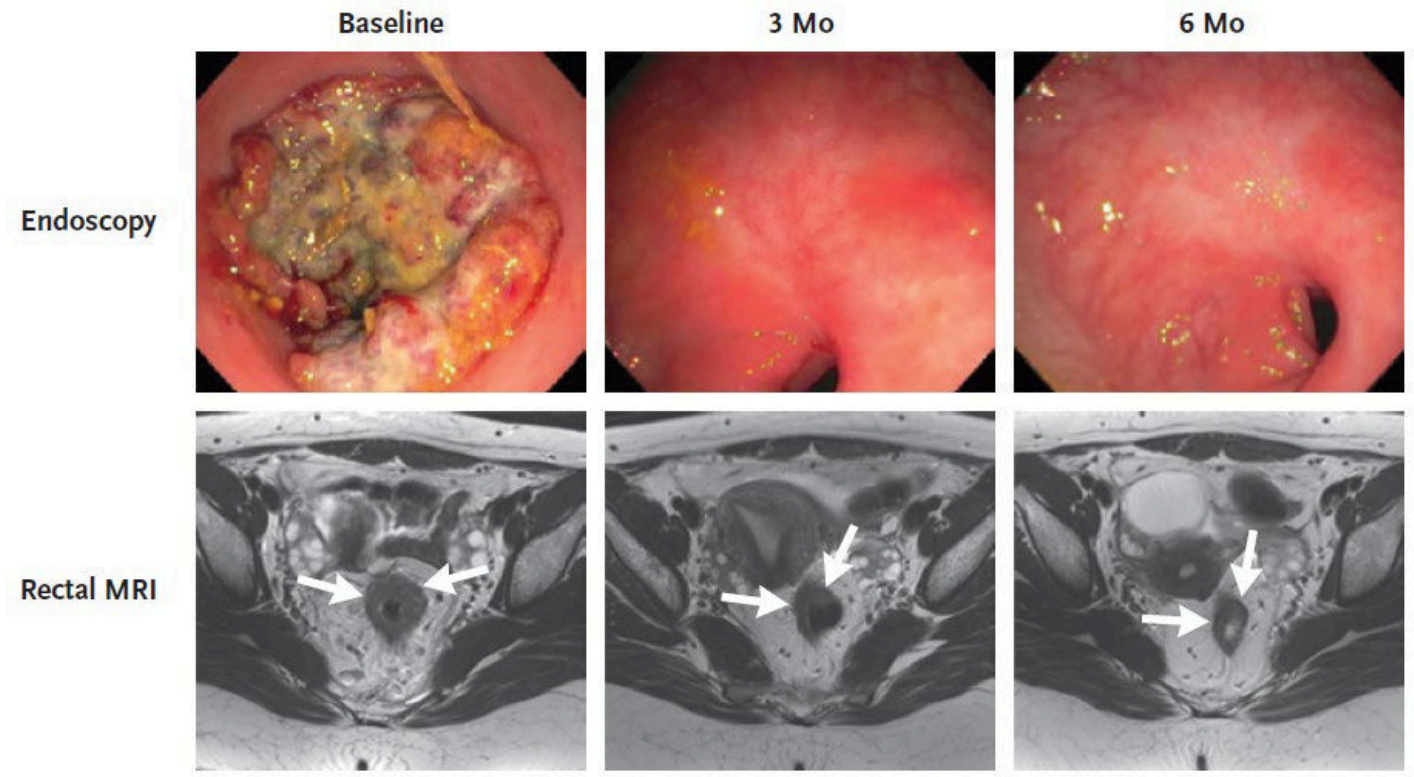
Memorial Sloan Kettering Cancer Center

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2022 VOL. 386 NO. 25

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.



Phase 2 Trial: Patients with MMR deficient Colorectal Cancers treated with anti-PD-1 (dostarlimab) x 6 mo

CR: 12/12 (100%) by 12 mo
FU: 6-25 mo
No Grade 3 or higher ASEs

None treated with surgery or radiation

Memorial Sloan Kettering Cancer Center

Targeted therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

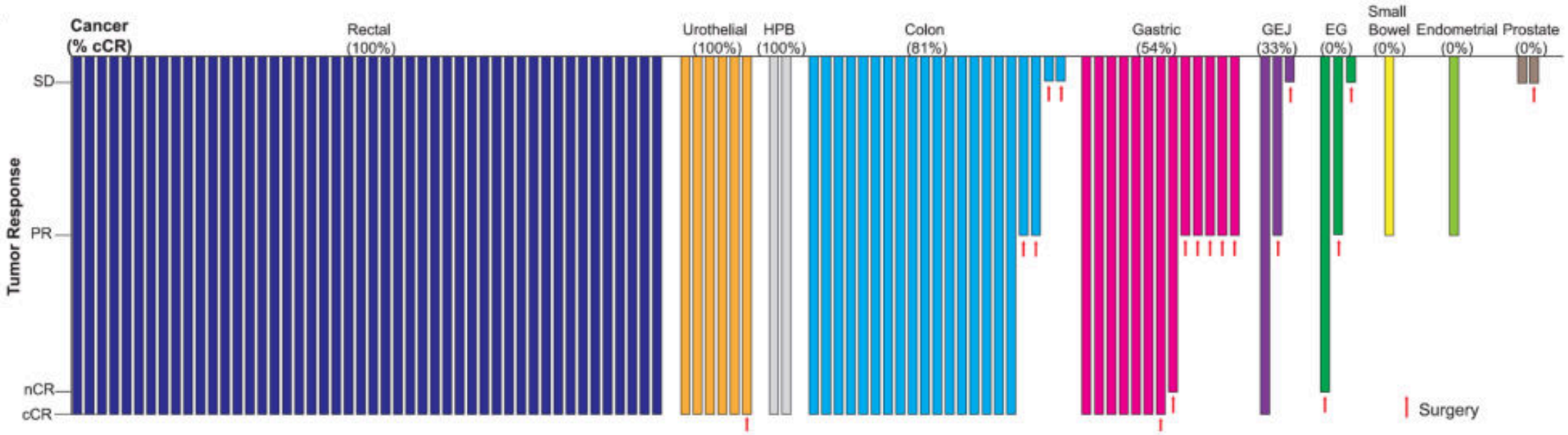
Nonoperative Management of Mismatch Repair–Deficient Tumors

A. Cercek,[1] M.B. Foote,[1] B. Rousseau,[1] J.J. Smith,[2] J. Shia,[3] J. Sinopoli,[1] J. Weiss,[1] M. Lumish,[4] L. Temple,[1] M. Patel,[1] C. Wilde,[1] L.B. Saltz,[1] G. Argiles,[1] Z. Stadler,[1] O. Artz,[1] S. Maron,[1] G. Ku,[1] P. Gu,[1] Y.Y. Janjigian,[1] D. Molena,[2] G. Iyer,[1] J. Coleman,[2] W. Abida,[1] S. Cohen,[1] K. Soares,[2] M. Schattner,[1] V.E. Strong,[2] R. Yaeger,[1] P. Paty,[2] M. Shcherba,[1] R. Sugarman,[1] P.B. Romesser,[5] A. Zervoudakis,[1] A. Desai,[1] N.H. Segal,[1] I. El Dika,[1] M. Widmar,[2] I. Wei,[2] E. Pappou,[2] G. Fumo,[6] S. Aparo,[7] M. Gonen,[8] M. Gollub,[9] V.S. Jayaprakasham,[9] T.-H. Kim,[9] J. Garcia Aguilar,[2] M. Weiser,[2] and L.A. Diaz, Jr.[1]

- Phase 2 trial
- Stage I, II, and III dMMR cancers
- Single agent anti-PD-1 dostarlimab
- Primary endpoint: complete response at 12 months

The NEW ENGLAND JOURNAL of MEDICINE

Nonoperative Management of Mismatch Repair–Deficient Tumors

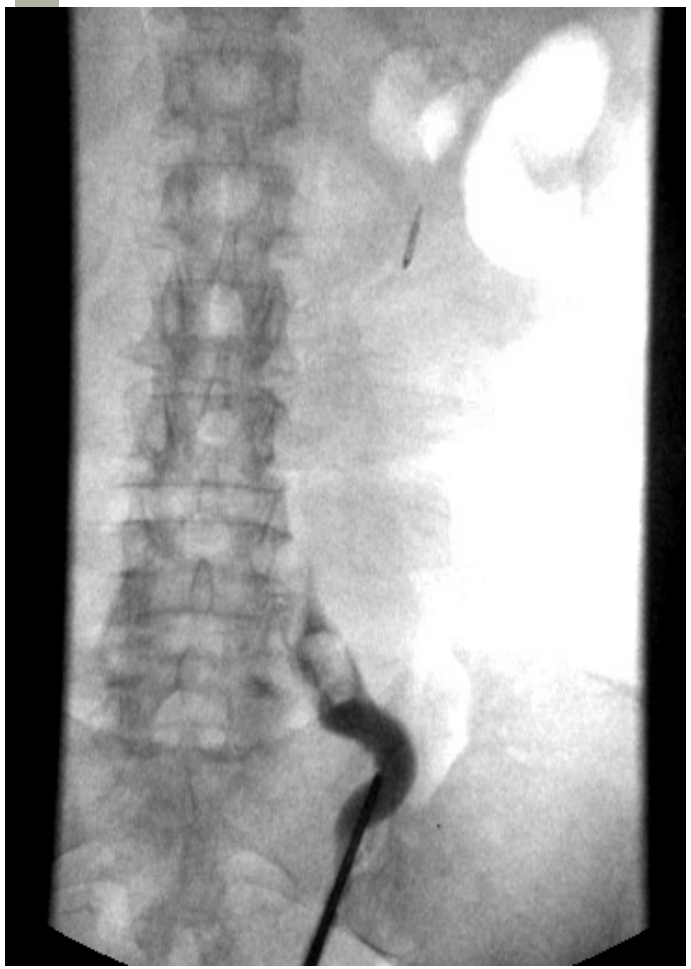


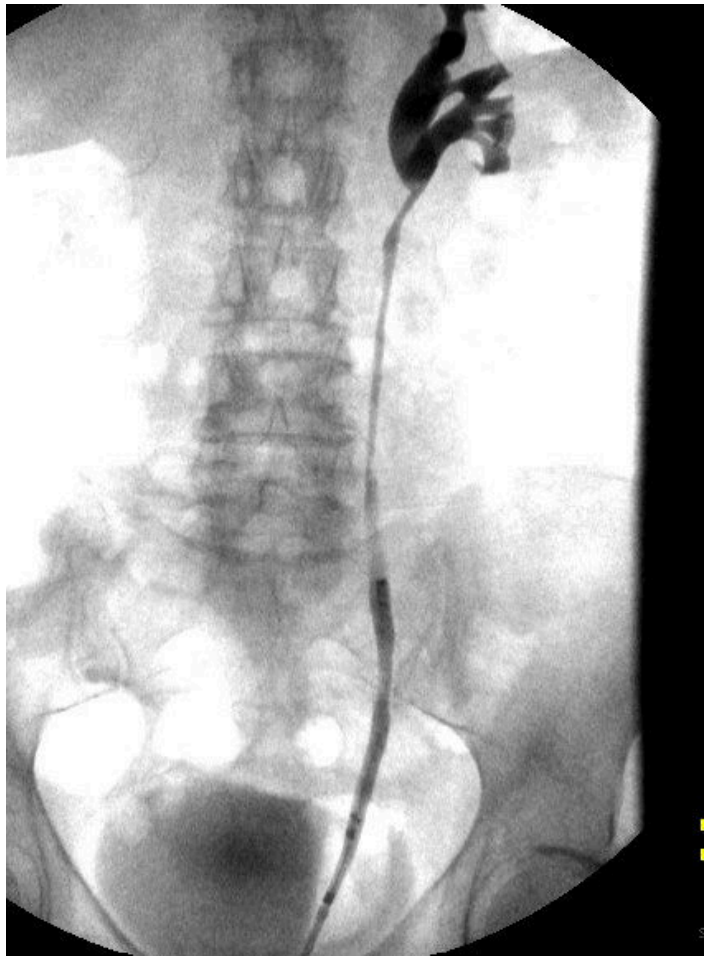
- PD1 blockade instead of surgery for MSI-High Cancers (N= 117 patients)
- Single Arm Trial; Dostarlimab (500mg IV every 3 weeks for 9 cycles)
- 6 Patients with UTUC – 100% Complete Response
- 5 Remain in long-term follow up, all NED and off therapy
- Toxicity: 4 grade 3 or 4 AEs (diabetes, pneumonia, encephalitis, neutropenia x 2)

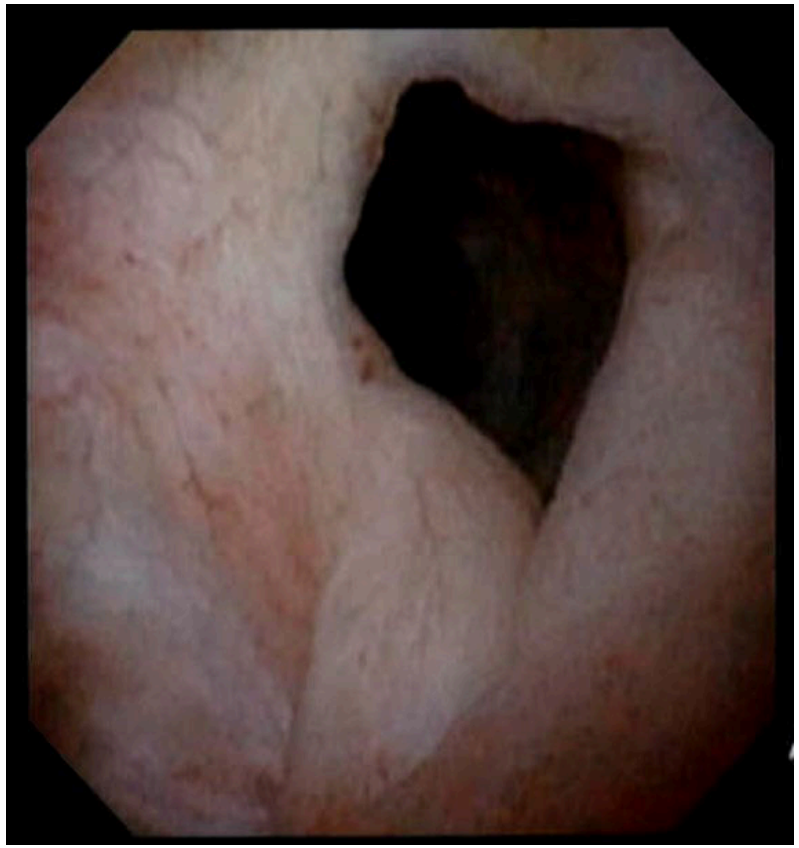
April 27, 2025 N Engl J Med 2025;392:2297-2308

Memorial Sloan Kettering Cancer Center

66 yo Woman, Newly Dxd UTUC, Endometrial Ca, Lynch Syndrome
Pre and Post Imaging – 3 Mos Dostarlimab (MSK 19-288)
5 years off therapy







Memorial Sloan Kettering Cancer Center

Targeted therapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Bladder Cancer

NCCN Guidelines Index
Table of Contents
Discussion

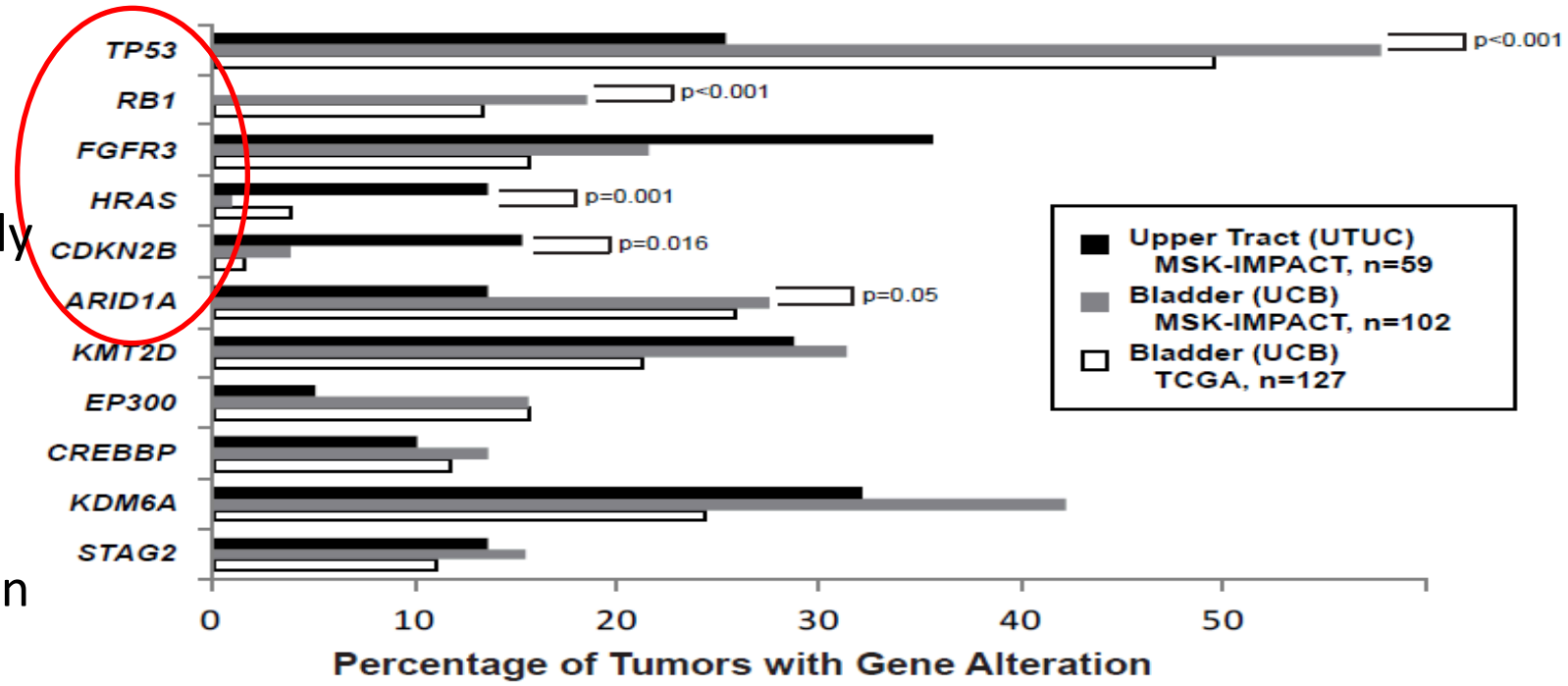
Biomarker-Directed Therapy (regardless of previous therapy) (pan-cancer tumor-agnostic treatments can be considered for patients with actionable mutations)
• Erdafitinib (susceptible *FGFR3* genetic alterations)[f,35] • Fam-trastuzumab deruxtecan-nxki (HER2-positive, IHC 3+)[36]

Loriot et al. NEJM. 2019. PMID: 31340094.

Memorial Sloan Kettering Cancer Center

Genomic Profile UTUC vs UCB

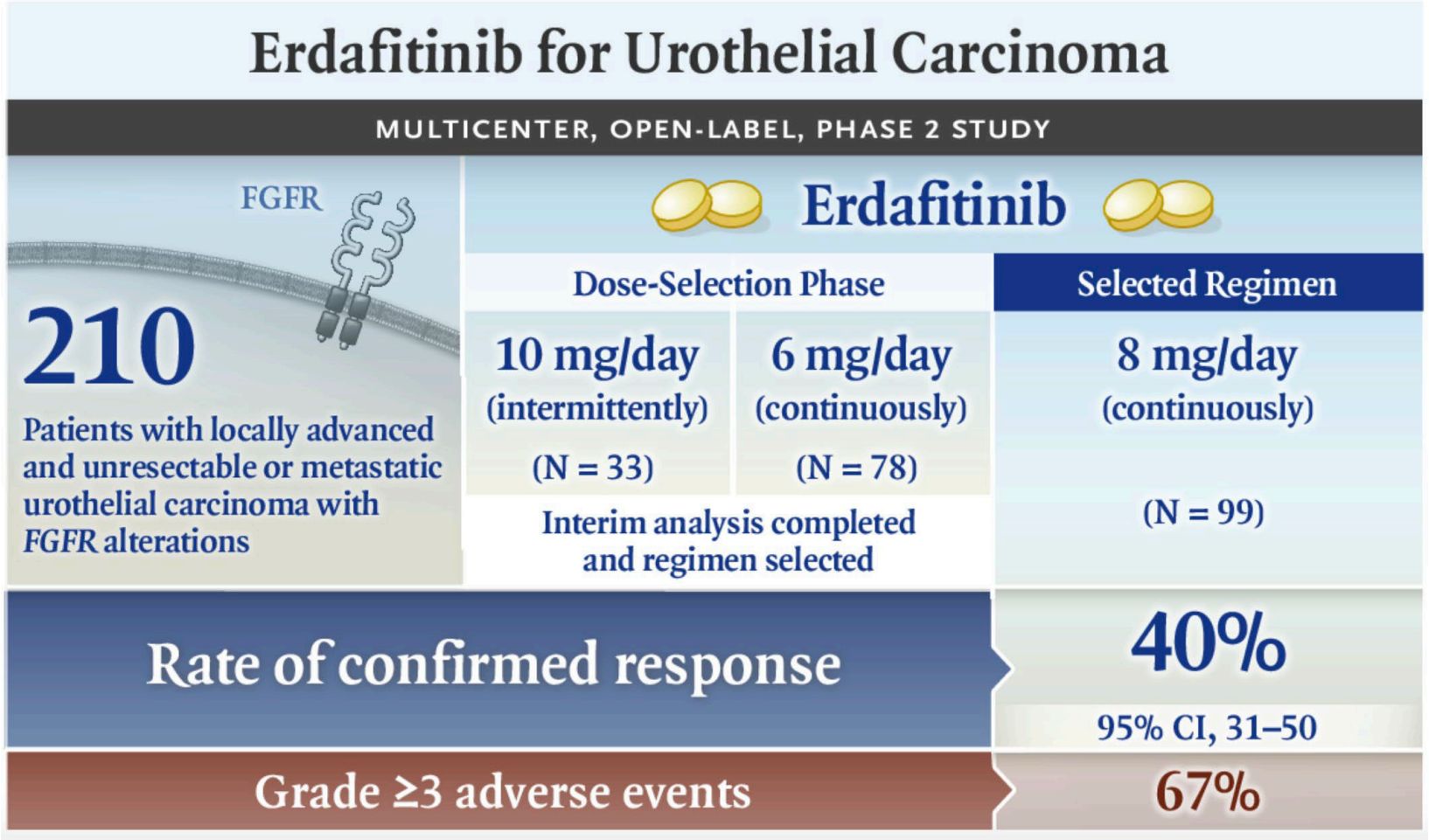
- Similar genes mutated in bladder cancer (UCB)
  - Except RB1
- Frequency of mutations significantly different in UTUC
  - ↑FGFR3, HRAS, CDKN2B
  - ↓TP53, RB, ARID1A
- Implies a subtle biologic difference between UTUC and UCB reflected in clinical behavior



Sfakianos, Cha et al (E Urol, 2015)

Memorial Sloan-Kettering Cancer Center

Targeted therapy



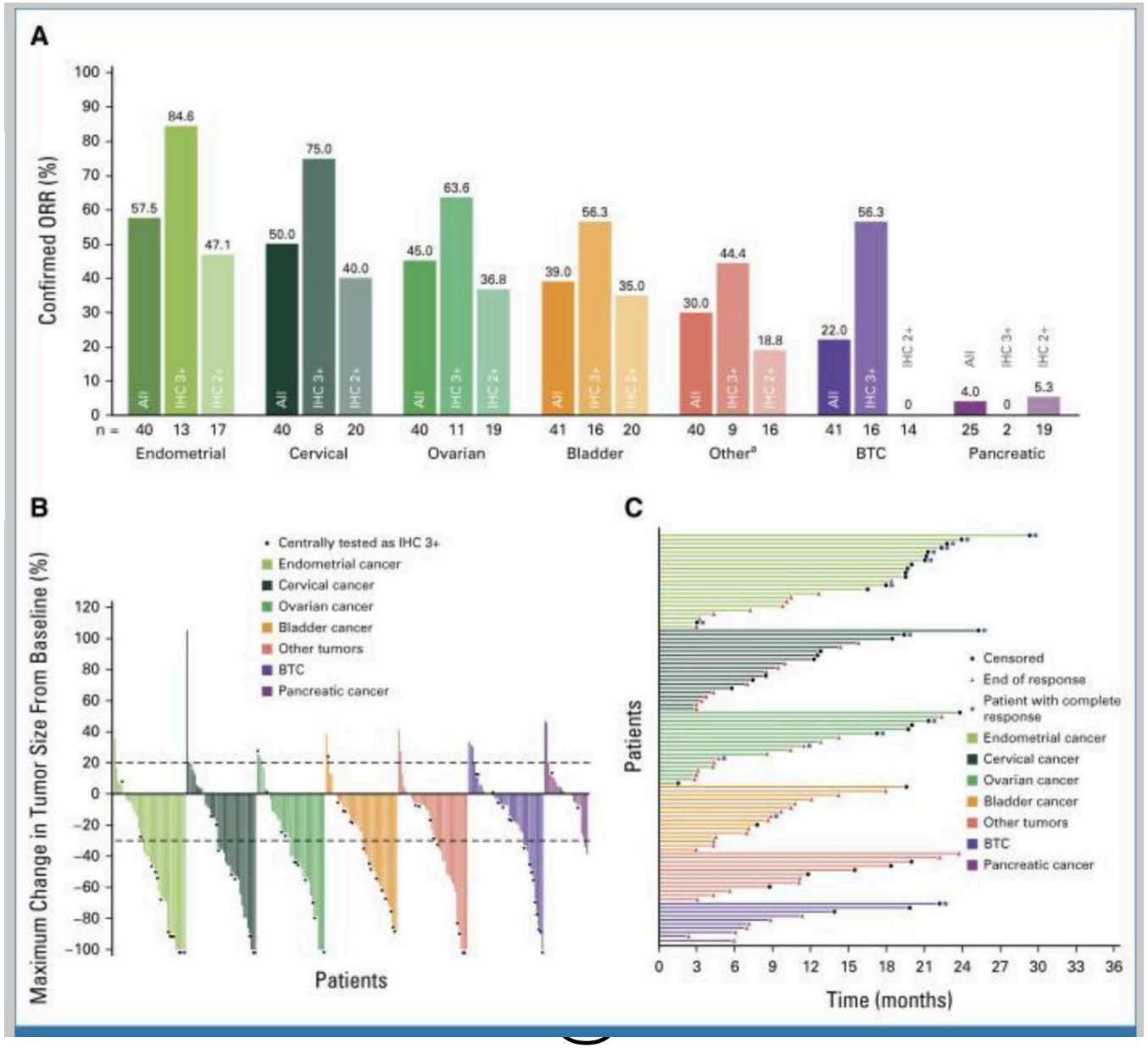
Loriot et al. NEJM. 2019. PMID: 31340094.

Targeted therapy

J Clin Oncol. 2023 Oct 23;42(1):47–58. doi: 10.1200/JCO.23.02005

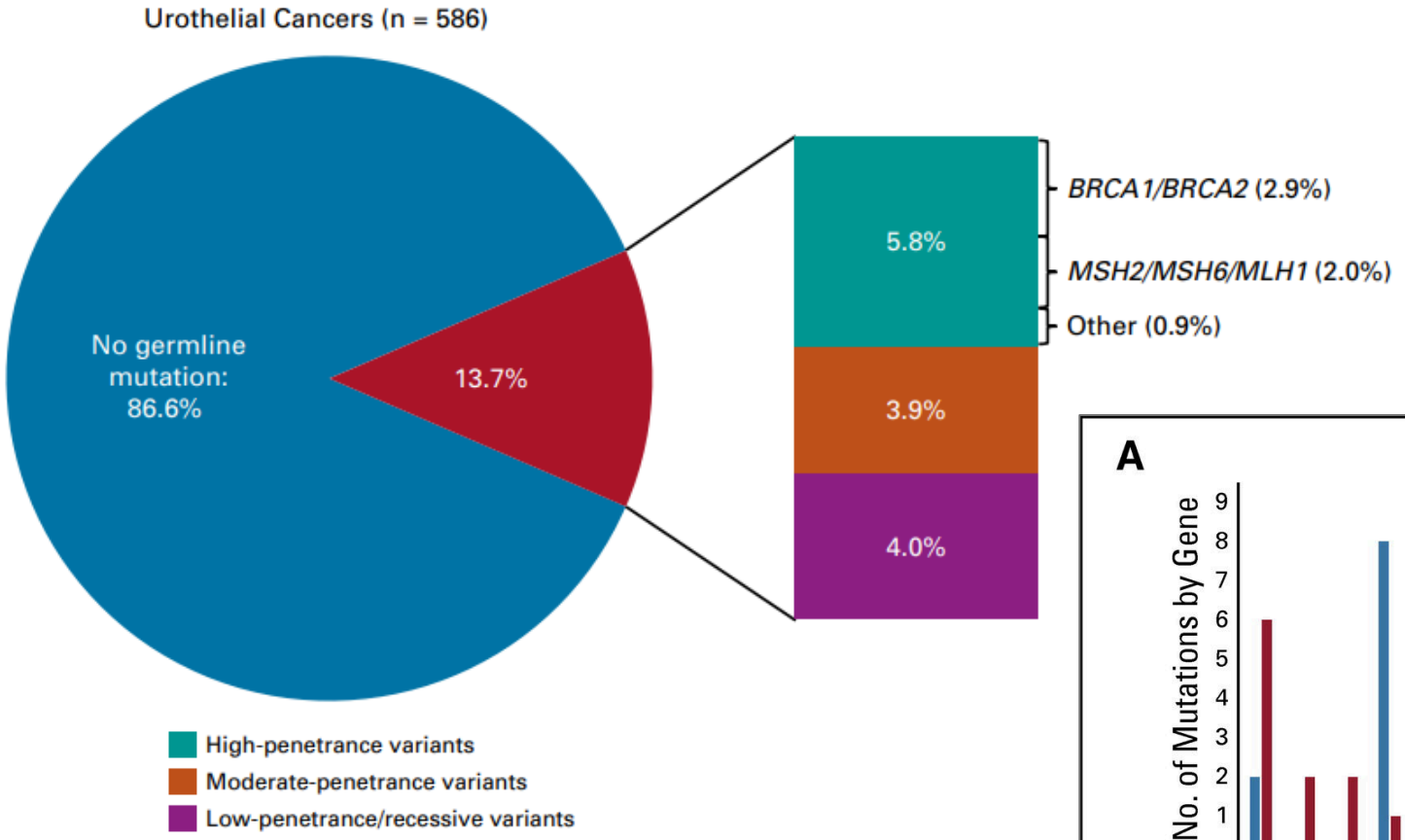
Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

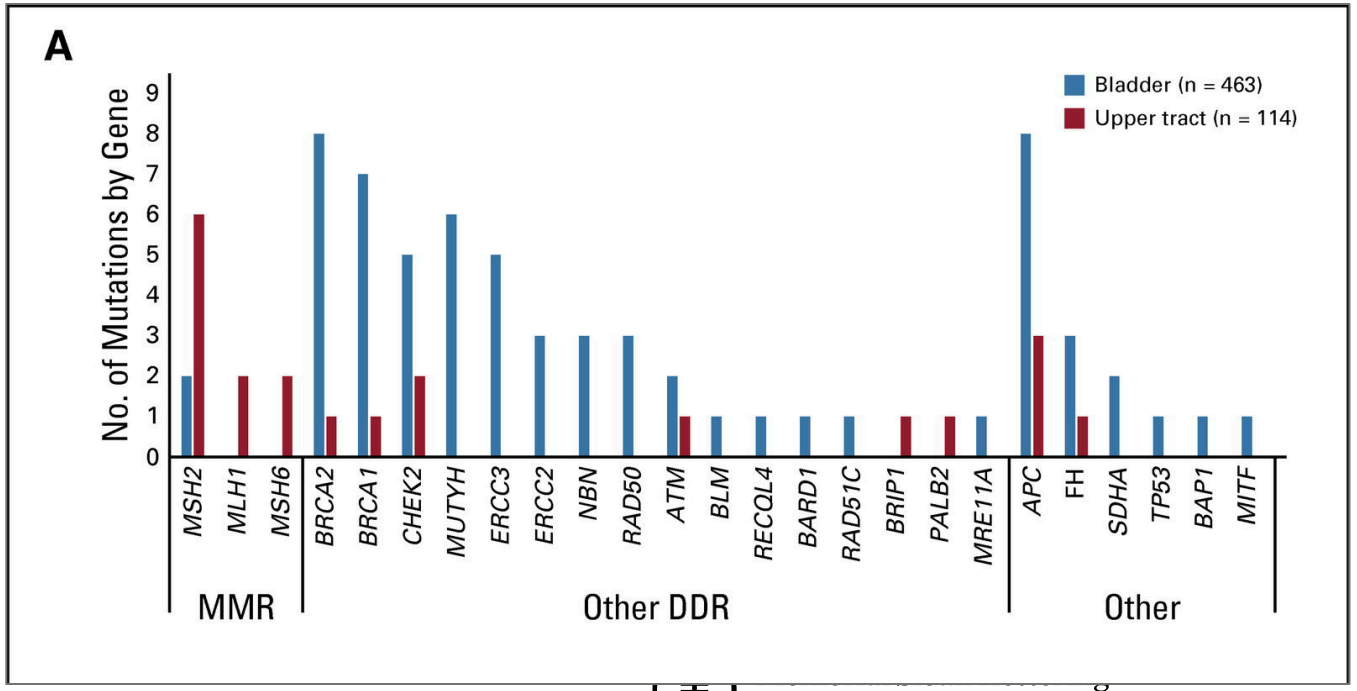
Funda Meric-Bernstam [1,✉], Vicky Makker [2,3], Ana Oaknin [4], Do-Youn Oh [5], Susana Banerjee [6], Antonio González-Martín [7], Kyung Hae Jung [8], Iwona Ługowska [9], Luis Manso [10], Aránzazu Manzano [11], Bohuslav Melichar [12], Salvatore Siena [13], Daniil Stroyakovskiy [14], Anitra Fielding [15], Yan Ma [16], Soham Puvvada [15], Norah Shire [15], Jung-Yun Lee [17]



What about other germline variants in urothelial cancers?

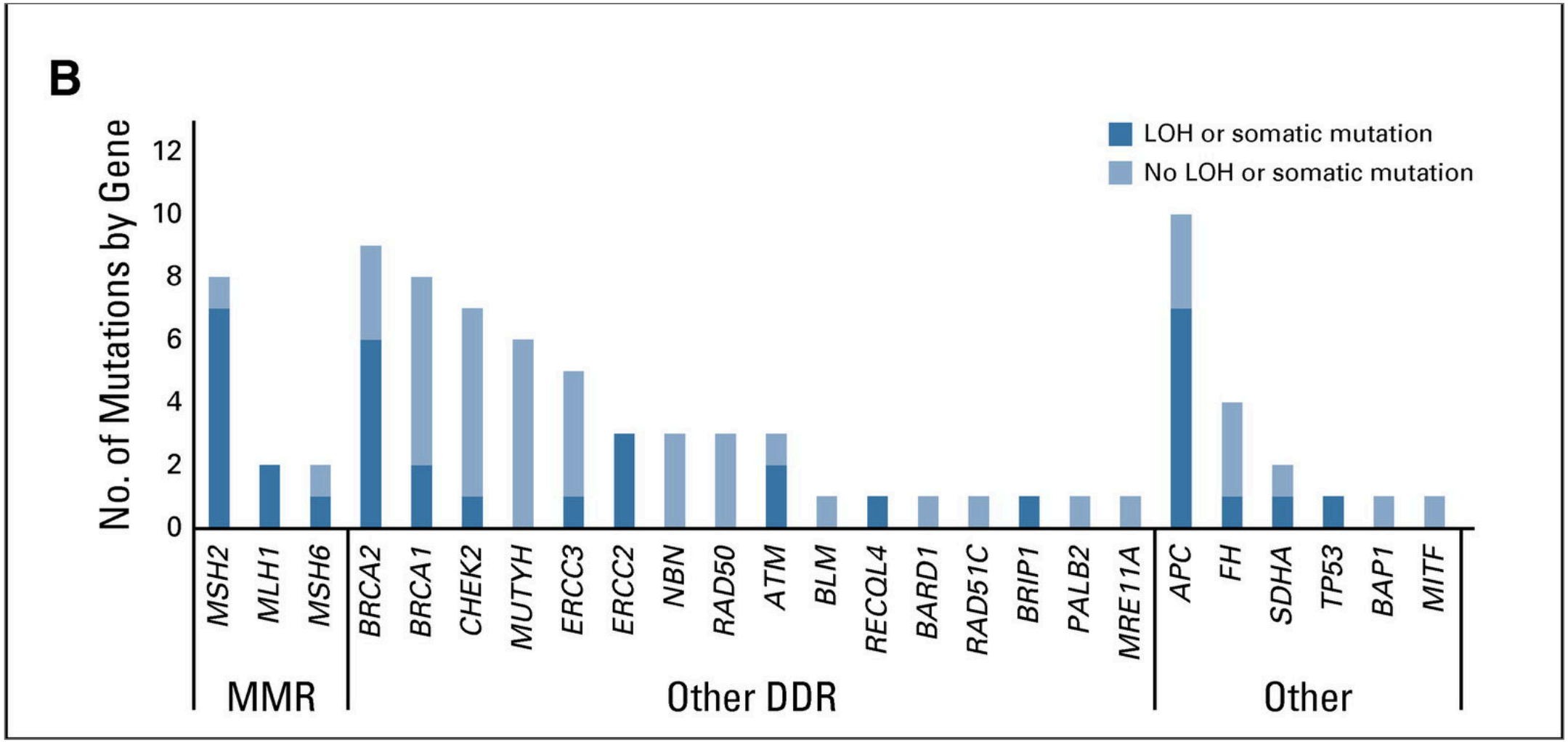
Germline genetics of urothelial carcinoma





Carlo et al. JCO 2020

Germline genetics of urothelial carcinoma



Carlo et al. JCO 2020

Memorial Sloan Kettering Cancer Center

Summary

- Lynch syndrome is associated with an increased risk of UTUC and likely bladder cancer, especially for carriers of *MSH2* mutations
- Better data is needed to guide optimal UC screening strategies in Lynch syndrome patients
- Possible UC increase risk with germline DNA-damage repair mutations (i.e. *BRCA2*)
- There may be a future role of genetic testing for systemic therapy choice or clinical trial enrollment
  - Immunotherapy in MSI-H tumors
  - FGFR3
  - PARP inhibitor and other trials

Adrenal and Renal Genetic Risk Assessment

Brian Shuch, MD
Professor of Urology,
Director, Kidney Cancer Program
Alvin & Carrie Meinhardt Endowed Chair
UCLA School of Medicine, Los Angeles, CA, USA

Pre-Test Questions

- Which of the following patients would NOT be automatically referred for genetic counseling/testing and require additional suspicion

A. A 72 year old man with a 3 cm pre-aortic paraganglioma

B. A 31 year old man with a 5 cm pheochromocytoma

C. A 11 year old girl with a 5.2 cm adrenocortical carcinoma

D. A 48 year old female with a 5 cm chromophobe RCC

Pre-Test Questions

- A 32-year-old woman is diagnosed with adrenocortical carcinoma (ACC). She has no significant family history of cancer. According to current guidelines, which is the next step regarding genetic evaluation?

- A. Test only for TP53 because it is the most common hereditary cause of ACC
- B. Recommend comprehensive germline testing, including TP53 and Lynch syndrome genes
- C. Genetic testing is only indicated for pediatric patients with ACC
- D. No genetic testing is needed unless a first-degree relative has ACC

Pre-Test Questions

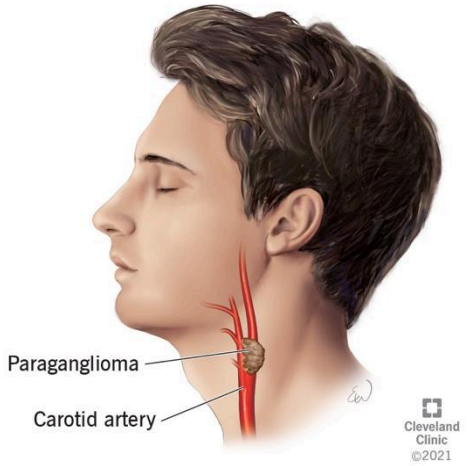
- A 27-year-old man with confirmed VHL disease is found with a new, asymptomatic 3.2 cm pheochromocytoma. He asks whether belzutifan could be used instead of surgery, noting that HIF-2α inhibitors are approved for metastatic pheochromocytoma. Which of the following is the most accurate recommendation?

- A. Belzutifan is appropriate as it can be used for any VHL tumor
- B. Belzutifan may delay surgery for adrenal masses but should only be used after biochemical testing
- C. Belzutifan is preferred over adrenalectomy for localized VHL pheochromocytoma
  D. Belzutifan is not indicated for adrenal tumors in VHL and should not be used for suspected pheochromocytoma

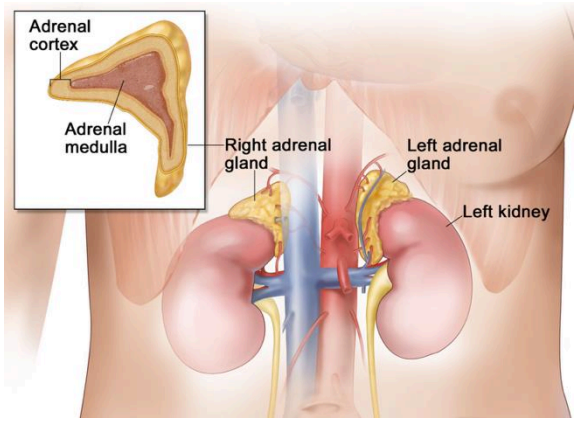
Why Genetics Matters in GU Oncology

- RCC and adrenal tumors have **higher hereditary cause** than previously recognized
- **Genetics drives management** in adrenal & renal tumors
  - **This is no longer purely academic**
- **Belzutifan** and other targeted agents require early identification
- Germline testing recommended more broadly (NCCN Guidelines 2024–2026)
- Tele-genetics & mainstreaming have removed access barriers

Hereditary Adrenal/Chromaffin Tumors



- Pheochromocytoma (85%) and Paraganglioma (15%)
- Rare Tumors with Annual US cases/year
  - -PCC: 1500; PGL:250, ACC: 300
- **All PCC and all PGL patients should undergo germline testing**
- Germline Component: PCC: 30–40% & PGL: ~60%
- Malignancy risk: PCC: 10–15% PGL: up to 30%



Paraganglioma (PGL)

- 80% of PGL's occur in the abdomen and pelvis
  - -1/2000 bladder tumors (micturation syncope)

- Functional variability
  - -Sympathetic derived (abdominal)- more likely secretory
  - -Parasympathetic derived (H&N)- silent

- Up to 30% of cases are malignant/metastatic

All patients with PGL should have genetic testing

PCC/PGL Germline Alterations

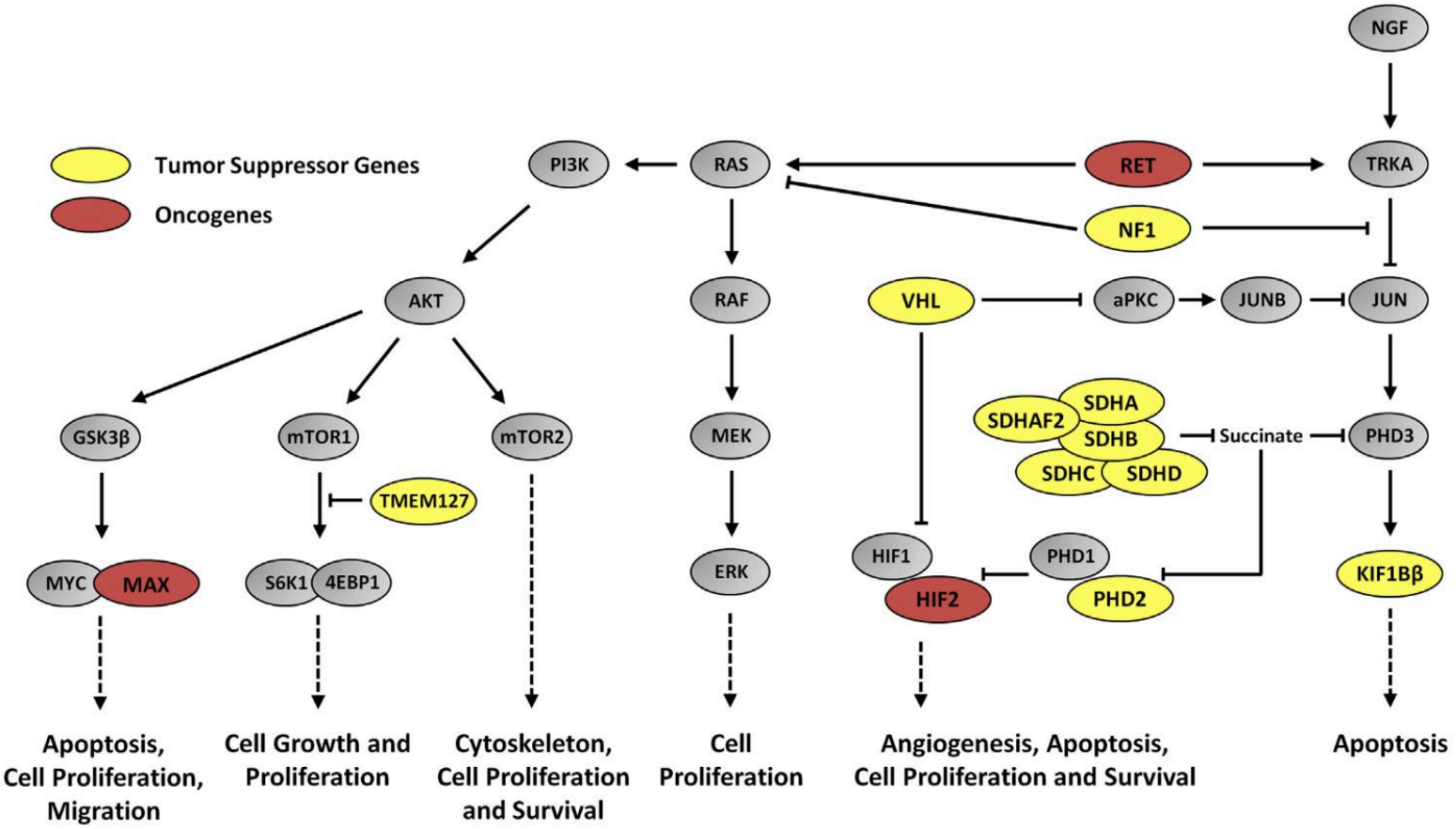


Table 2. Characteristics of Pheochromocytoma-Associated Syndromes.*

Gene	Syndrome	Nonchromaffin Tumors	Transmission	Adrenal Tumors	Head and Neck Tumors	Extraadrenal Tumors†	Multiple Tumors	Metastatic Tumors‡	Family History§
				frequency (percent)					
VHL	VHL	Retinal and CNS hemangioblastomas, RCC, pancreatic neuroendocrine tumor, ELST	Autosomal dominant	>50	<1	10–24	>50	1–9	25–50
NF1	NF1	Cutaneous neurofibromas, malignant peripheral-nerve-sheath tumor, breast cancer	Autosomal dominant	>50	<1	1–9	25–50	1–9	10–24
RET	MEN-2	Medullary thyroid carcinoma, hyperparathyroidism	Autosomal dominant	>50	<1	<1	>50	<1	25–50
SDHA	PGL5	Rarely also pituitary adenoma, GIST, RCC	Autosomal dominant	25–50	25–50	25–50	1–9	1–9	1–9
SDHB	PGL4	Rarely also pituitary adenoma, GIST, RCC	Autosomal dominant	25–50	25–50	25–50	10–24	25–50	10–24
SDHC	PGL3	Rarely also pituitary adenoma, GIST	Autosomal dominant	1–9	>50	<1	10–24	Not reported	10–24
SDHD	PGL1	Rarely also pituitary adenoma, GIST, RCC	Autosomal dominant, maternal imprinting	10–24	>50	10–24	>50	1–9	25–50
SDHAF2	PGL2		Autosomal dominant, maternal imprinting	1–9	>50	Not reported	>50	Not reported	>50
MAX	No name	Rarely also RCC	Autosomal dominant	>50	<1	1–9	>50	1–9	25–50
TMEM127	No name		Autosomal dominant	>50	1–9	<1	25–50	10–24	1–9

Fumarate Hydratase now implicated in PCC

Neumann, H. P. H., Jr., W. F. Y. & Eng, C. Pheochromocytoma and Paraganglioma. *New Engl J Med* **381**, 552–565 (2019).
Zavoshi, S. *et al.* Fumarate Hydratase Variants and their Association with Paraganglioma/Pheochromocytoma. *Urology* (2023), ePub

Adrenocortical Carcinoma (ACC)

- ~300 cases a year in the US (~5-10% in children)
- Aggressive
  - -Median size of diagnosis is 10 cm and 50% stage 3/4
  - -20% 5-year survival with invasive/metastatic disease
- 60% of cases have endocrine hypersecretion
- ~10-15% of cases linked to a germline predisposition
- *Early identification, testing, screening save lives*

Petr, E. J. & Else, T. Adrenocortical carcinoma (ACC): When and why should we consider germline testing? *La Press Médicale* **47**, e119–e125 (2018).

ACC Genetic Testing

- 50% of Children with ACC have genetic factors[5]
  - -Li-Fraumeni Syndrome (LFS)-*TP53*
  - -Beckwith-Wiedemann (IGF2 overexpression) and hemi-hyperplasia
- Adults with ~10% germline factors
  - -unselected series 7.5% carried germline mutation[6]
  - -Lynch syndrome may predispose (MLH1, MSH2, MSH6, PMS2)
  - -Brazilian TP53 p. R337H founder mutation very common
- *Genetic testing increasingly recommended universally especially for LFS and Lynch Syndrome*

5. Wasserman JD, et al. J Clin Oncol 33 (6): 602-9, 2015
6. Raymond, V. M. *et al.*. **98**, E119–E125 (2013).

Syndromes associated with ACC and their characteristics

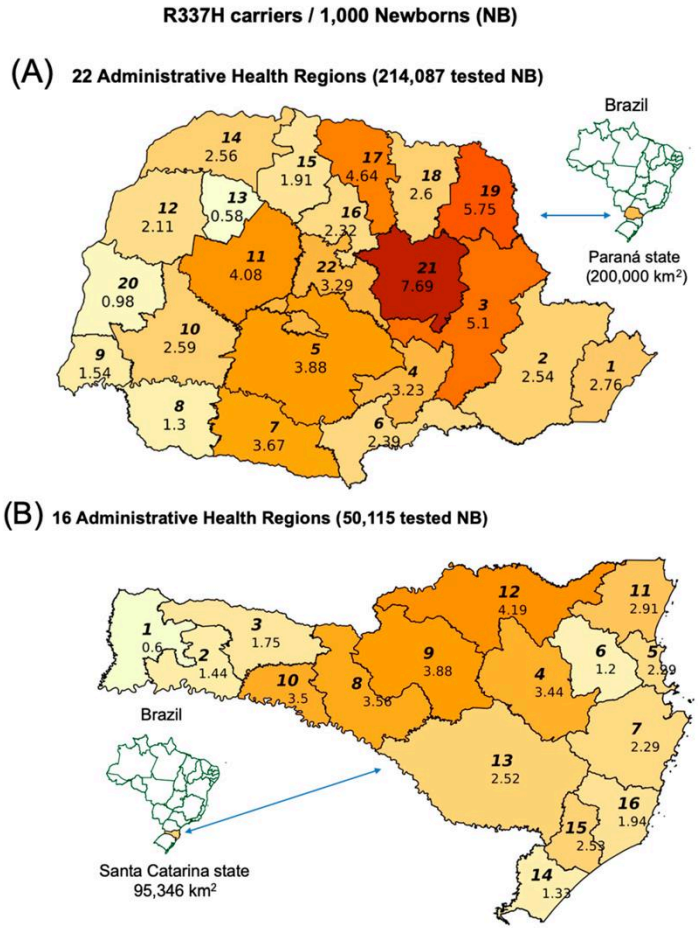
Syndrome	Gene(s)	Prevalence	Prevalence of ACC	Other adrenal phenotype	Other associated features
Common					
Li-Fraumeni (LFS)	TP53	1:20,000 to 1:1,000,000	50–80% of children; 3–7% of adults	n/a	Brain cancer, breast cancer, lung cancer, sarcoma, leukemia, choroid plexus tumor
Lynch (LS)	MSH2, MLH1, PMS2, MSH6, EPCAM	1:440	3% of adults	n/a	Colorectal, endometrial, small bowel, ureteral cancer, sebaceous carcinoma, pancreas cancer, prostate cancer
Rare					
MEN1	MENIN	1:30,000	1–2% of adults	Adrenal enlargement, adrenal adenomas	Pituitary adenomas, primary hyperparathyroidism, pancreatic neuroendocrine tumors, other foregut neuroendocrine tumors
FAP	APC	1:30,000	Rare, case reports	Adrenal adenomas	Colon cancer, duodenal adenomas, thyroid cancer
Beckwith-Wiedemann	IGF2 locus	1:13,000	Rare, case reports; occur in childhood only	Benign adrenal cysts and adenomas	Cancers in childhood, Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma
Very rare/case reports					
NF1	NF1	1:3,000	Rare, case reports, can occur in young children	n/a	Gliomas, malignant nerve sheath tumor, benign neural tumors
Carney Complex	PRKAR1A	Rare > 700 patients in the world	Rare, case reports	PPNAD	Pituitary and thyroid tumors, cardiac myxomas, schwannomas and other tumors

Petr, E. J. & Else, T. Adrenocortical carcinoma (ACC): When and why should we consider germline testing? *La Press Médicale* **47**, e119–e125 (2018).

Highly prevalent *TP53* mutation predisposing to many cancers in the Brazilian population: a case for newborn screening?

Maria Isabel Waddington Achatz, Pierre Hainaut, Patricia Ashton-Prolla

The unusually high population frequency of a germline *TP53* mutation (R337H) predisposing to early cancer has led to mass newborn testing for this mutation in the State of Paraná, southern Brazil. Newborn screening for inherited cancer risk is complex and controversial. In this paper, we discuss the justifications for this screening by considering the medical and scientific evidence for this mutation. R337H has been identified in Brazilian families with Li-Fraumeni or related syndromes predisposing to cancers in childhood (ie, brain, renal, and adrenocortical carcinomas), adolescence (ie, soft tissue and bone sarcomas), and young adulthood (ie, breast cancer). R337H has also been detected in children with adrenocortical carcinoma without a documented family history of cancer. The mutation is estimated to occur in about 0·3% of the population in southern Brazil and is associated with increased cancer risk throughout life. Cancer patterns in families positive for R337H suggest strong genetic modifying effects, making it difficult to predict individual risk. Because protocols for cancer-risk management in Li-Fraumeni or related syndromes are debatable, extreme care should prevail in predictive testing of children for R337H. A detailed assessment of the risks, benefits, and costs is needed to ensure that medical, social, and ethical justifications for newborn screening are met.



- 0.3% of population in Southern Brazil
- The ACT penetrance in PR for probands followed from birth to 12 years was 3.9%
- Routine surveillance (PE, imaging, labs) for ACC

David Geffen School of Medicine

Achatz, et al. *Lancet Oncol* **10**, 920–925 (2009).
Costa, T. E. J. *et al. Cancers* **11**, 1804 (2019).

UCLA Health

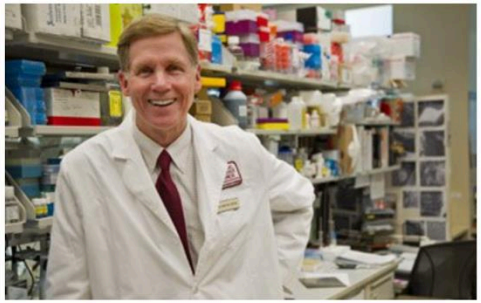
Hereditary Cancer and the Kidney

- "2-8% of RCC" believed hereditary cited but not based on evidence
- Now >15+ recognized genes associated with RCC syndromes
- There is an even stronger inheritance pattern (twin studies and registries)
  -various risk alleles identified
- FLCN and FH are incredibly common!!
- Management may be dictated by the presence of a germline alteration

Unlike the adrenal lesions, there are 35X more RCC cases annually, so not feasible to refer all, unless you want an angry genetic counselor….

The Long Road to Understanding Kidney Cancer

W. Marston Linehan investigates kidney cancer gene pathways to find new treatment strategies.



Dr. Linehan in the lab.

When W. Marston Linehan, M.D., came to the NIH more than 30 years ago, doctors thought of kidney cancer as a single disease. There was no effective therapy for its advanced stages, and 80 percent of patients with advanced kidney disease died within two years. Since then, Linehan has found new understandings of the numerous cancers occurring in the kidney. In addition, he has led novel approaches to treating both sporadic (non-inherited) and familial (inherited) forms of the diseases.

In the early 1980s, Linehan and Berton Zbar, M.D., began studying tumors from patients with sporadic kidney cancer, aiming to identify a kidney cancer gene that could lay a foundation for developing a targeted therapy. With tissue from those tumors, the team found an abnormality on chromosome 3 that they suspected might indicate the presence of a kidney cancer gene.

Postdoctoral fellow Christopher Ricketts, Ph.D., prepares samples for analysis.

"Unfortunately, we came to the sad realization that, with my laboratory working 13 hours a day and six days a week and his lab working 13 hours a day and six days a week, and with the tools available to us at the time, we could find the kidney cancer gene in this location on chromosome 3 within … about … 54-and-a-half years," Linehan says.

Hereditary RCC's Often Hide in Plain Sight

If you don't look for it, you won't find it….

2022 WHO Renal Tumor Categorization:

Designation of Hereditary Categories But Most Hide Within Subtypes

Table 1. Renal cell tumours in the WHO 2022 classification

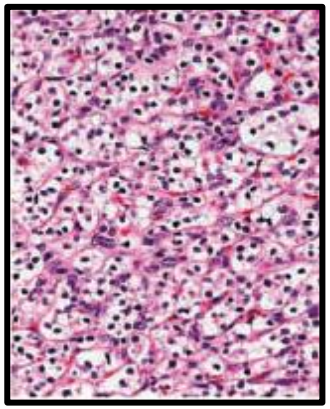
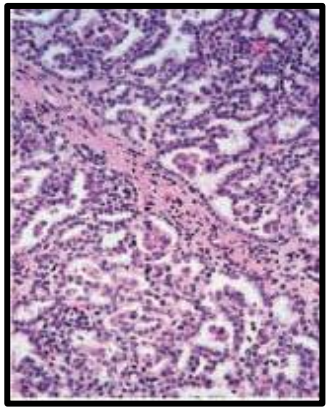
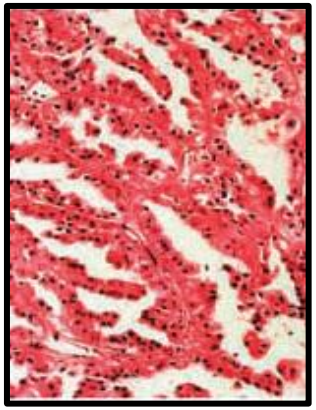
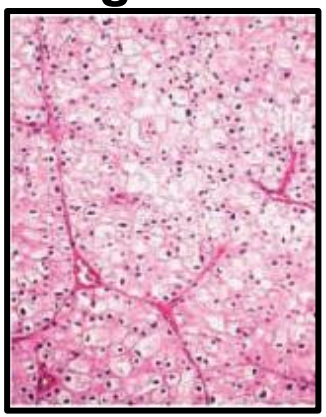
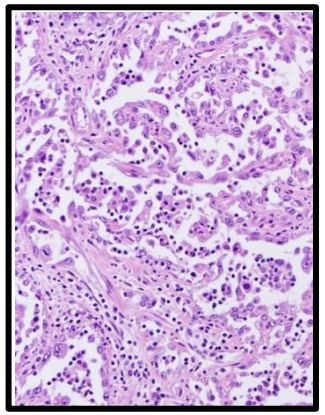
Renal cell tumours
Clear cell renal cell tumours
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal tumours
Renal papillary adenoma
Papillary renal cell carcinoma
Oncocytic and chromophobe renal tumours
Oncocytoma of the kidney
Chromophobe renal cell carcinoma
Other oncocytic tumours of the kidney
Collecting duct tumours
Collecting duct carcinoma
Other renal tumours
Clear cell papillary renal cell tumour
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Eosinophilic solid and cystic renal cell carcinoma
Renal cell carcinoma NOS
Molecularly defined renal carcinomas
TFE3-rearranged renal cell carcinomas
TFEB-altered renal cell carcinomas
ELOC (formerly TCEB1)-mutated renal cell carcinoma
Fumarate hydratase-deficient renal cell carcinoma
Succinate dehydrogenase-deficient renal cell carcinoma
ALK-rearranged renal cell carcinomas
SMARCB1-deficient renal medullary carcinoma
Emerging/provisional entities (still not part of the classification as definitive entities)
Biphasic squamoid alveolar renal cell carcinoma (discussed in the *Papillary renal cell carcinoma* chapter)
Biphasic hyalinising psammomatous renal cell carcinoma (discussed in the *Introduction* chapter)
Papillary renal neoplasm with reverse polarity (discussed in the *Papillary renal cell carcinoma* chapter)
Warthin-like papillary renal cell carcinoma (discussed in the *Papillary renal cell carcinoma* chapter)
Thyroid-like follicular carcinoma (discussed in the *Introduction* chapter)
Eosinophilic vacuolated tumour (discussed in the *Other oncocytic tumours of the kidney* chapter)
Low-grade oncocytic tumour (discussed in the *Other oncocytic tumours of the kidney* chapter)

NOS, not otherwise specified.

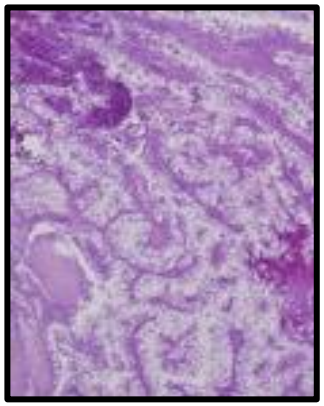
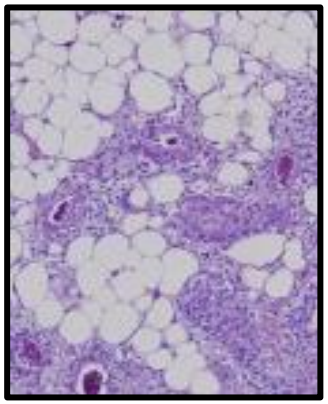
Raspollini MR, Moch H, Tan PH, Amin MB, Turajlic S. Renal cell tumours: Introduction. In WHO Classification of Tumours online, WHO Classification of Tumours Editorial Board eds. WHO classification of urinary and male genital tumours. 5th (beta version). Lyon: IARC Press, 2022 WHO Classification of Tumours

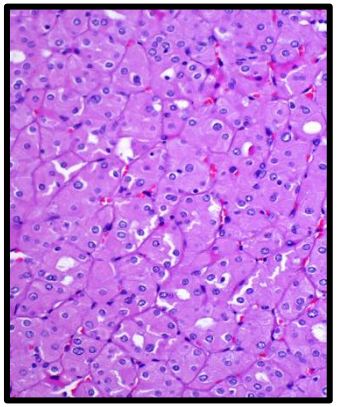
KCP
UCLA KIDNEY CANCER PROGRAM

"Sporadic Appearing" Renal Cancers And Potential Hereditary Background

Type:	Clear Cell	Papillary 1	Papillary 2	Chromophobe	Collecting Duct
Gene:	VHL SDHC BAP1	MET PTEN MITF	FH	FLCN PTEN	FH



Type:	Translocation	Angiomyolipoma	Oncocytic	Low Grade Onc (LOT)
Gene:	*TFE3,TFEB, MITF*	*TSC1,TSC2*	*SDHB, SDHD*	*TSC1/2*

Slide Adapted from Linehan

Kidney Cancer Genetic Syndromes

Table 1. Description of Known Hereditary Kidney Cancer Syndromes

Syndrome	Gene	Chromosome Location	Lifetime RCC Risk (%)	Other Manifestations	Histology
VHL syndrome	*VHL*	3p25	30-40	Retinal and CNS hemangioblastomas, pancreatic cysts and neuroendocrine tumors, pheochromocytomas, endolymphatic sac tumors, broad ligament and epididymal cystadenomas	Clear cell
HPRC	*MET*	7q31	100	None	Papillary type 1
HLRCC	*FH*	1p42	15-32	Cutaneous leiomyomas, uterine fibroids, adrenal nodules	Tubulocystic papillary (now known as HLRCC)
BHD syndrome	*FLCN*	17p11	30	Cutaneous fibrofolliculomas, pneumothorax, parotid gland oncocytomas	Hybrid oncocytic, chromophobe, oncocytoma
TSC	*TSC1/2*	9q34/16p13	< 5	Renal angiomyolipomas, angiofibromas, hypomelanotic macules, shagreen patches, subependymal giant-cell astrocytoma, seizures, oral mucosal lesions	Clear cell, papillary, and chromophobe
Cowden syndrome	*PTEN*	10q23	10-15	Macrocephaly, breast cancer and fibrocystic change, thyroid cancer, endometrial cancer, prostate cancer, colonic polyps, facial trichilemmomas	Clear cell, papillary, and chromophobe
Hereditary pheochromocytoma and paraganglioma	*SDHB/C/D*	1p36/1q23/11q23	< 10	Pheochromocytoma, paraganglioma, GI stromal tumor	Clear cell, unclassified/ eosinophilic variant
Chromosome 3 translocation syndrome	—	Translocations (3:6,3:8,3:11)	30	None	Clear cell
Hyperparathyroid jaw tumor syndrome	*CDC73*	1q31.2	Uncommon, likely < 10	Hyperparathyroidism, parathyroid cancer, jaw fibroma, uterine cancer	RCC and Wilms
BAP1 cancer syndrome	*BAP1*	3p21	9-13	Uveal and cutaneous melanoma and malignant pleural mesothelioma	Clear cell
MITF cancer syndrome	*MITF*	3p14	Uncommon, likely < 10	Melanoma, pancreatic cancer, pheochromocytoma	Not yet described; likely clear cell papillary–like translocation RCC

Abbreviations: BHD, Birt-Hogg-Dube; HLRCC, hereditary leiomyomatosis and renal cell cancer; HPRC, hereditary papillary renal cell cancer; MITF, microphthalmia-associated transcription factor; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.

Shuch, B. & Zhang, J. Genetic Predisposition to Renal Cell Carcinoma: Implications for Counseling, Testing, Screening, and Management. *Journal of Clinical Oncology* JCO2018792523 (2018)

Germline Mutations Causing RCC May NOT be Rare

Estimation of the Carrier Frequency of Fumarate Hydratase Alterations and Implications for Kidney Cancer Risk in Hereditary Leiomyomatosis and Renal Cancer

Brian Shuch, MD [1,2]; Shantao Li, PhD[3,4,5]; Harvey Risch, PhD[6]; Ranjit S. Bindra, MD, PhD[7]; Patrick D. McGillivray, MD[3]; and Mark Gerstein, PhD[3,4,5]

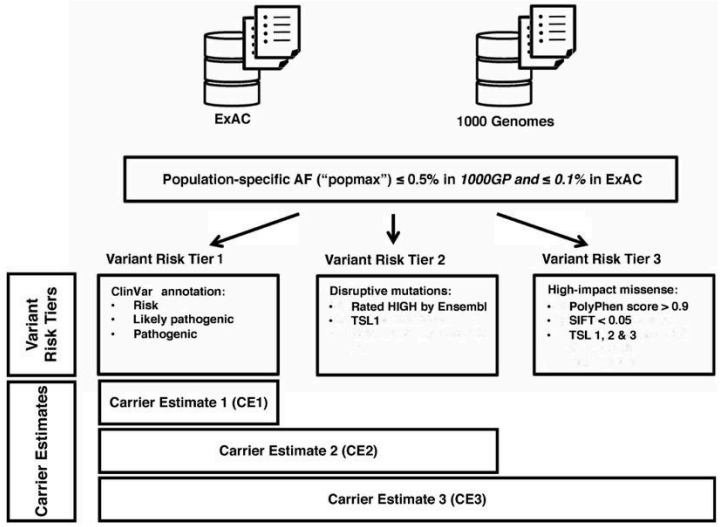
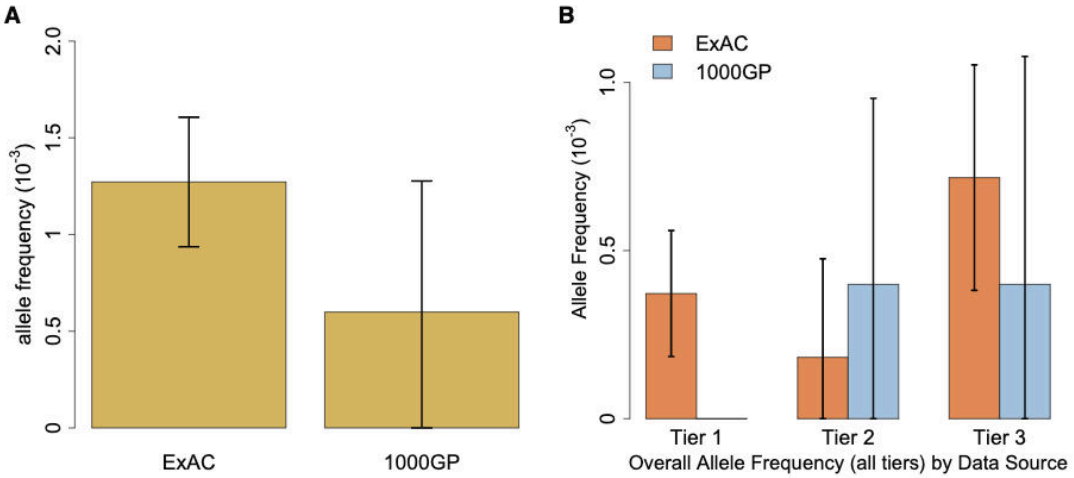


FIGURE 1. Fumarate hydratase variant classification scheme. 1000GP indicates 1000 Genomes Project; AF, allele frequency; ExAC Exome Aggregation Consortium; PolyPhen, Polymorphism Phenotyping; SIFT, Sorting Intolerant From Tolerant; TSL, transcript support level.



- *Analysis of databases demonstrate FH pathogenic variants very common (~1/1500)*
- *Follow-up Report from 120,000 Invitae patients demonstrates similar results*
- *Geisenger MyCode shows similar results in FLCN, 60X more common that estimates*

Shuch, B. *et al. Cancer* **59**, 86 (2020).
Savatt, J. M. *et al.*. *Genet Med* **24**, 1857–1866 (2022).

Estimation of Germline Alterations in Kidney Cancer

Series	Cohort/ Testing	Population	Cohort	RCC Associated Genes	Expanded Gene Set	Journal
Nguyen*	Ambry	All RCC / RenalNext	1235	6.1%	-	Cancer 2017
Carlo	MSKCC	Advanced RCC	211	5.5%	16.1%	JAMA Onc 2018
Hartman	Ambry	RCC Age < 60	844	3.7%	12.8%	Scientific Reports 2020
Abou Alawai	DFCI	Any RCC	1829	5.1%	17.0%	Cell Reports 2021
Wu	Fudan, China	RCC <46	190	6.3%	9.8%	Cancer 2019
Smith	Cambridge, UK	RCC <46, 2+ tumors <60, family history, negative Renal Genes	119	-	16.1%	Genes Chrom Cancer 2021

-Enriched cohorts above, significantly biased
-Unclear role of other genes like *CHEK2 (LOF), ATM, BRCA1/2, etc.*
-Unselected cohorts estimate 4-6% (2/3rd RCC genes)

Yngvadottir, B. *et al. Hum Mol Genet* **31**, (2022).
Sekine, Y. *et al. Hum Mol Genet* **31**, 1962–1969 (2022).

Red Flags to Consider Risk Assessment

- No universally accepted consensus
- Specific features are useful for selection for individuals

Early age of RCC diagnosis ≤45 years
Bilateral renal cancer (especially young)
Multifocal renal cancer
Strong family history of RCC (≥2 relatives in same blood line)
RCC with a) personal of family history of ≥1 tumor types*
Unusual Skin Conditions (ex. Leiomyomas, Fibrofolliculomas, Angiofibromas)
Family history of a Kidney Cancer Syndrome

*pheochromocytoma, brain/spinal hemangioblastoma, pancreatic neuroendocrine tumors, retinal tumors, papillary cystadenoma, endolymphatic sac tumor, GI stromal tumors, uterine fibroids (≤35 years of age), uveal and cutaneous melanoma, and solid cancers occurring in childhood

- Specific histologic findings**. (FH/SDH deficient/HOCT)

Genetic Risk Assessment for Hereditary Renal Cell Carcinoma: Clinical Consensus Statement

Gennady Bratslavsky, MD[1]; Neil Mendhiratta, MD, MS [2]; Michael Daneshvar, MD, MS[1,3]; James Brugarolas, MD, PhD[4]; Mark W. Ball, MD [3]; Adam Metwalli, MD[5]; Katherine L. Nathanson, MD[6,7]; Phillip M. Pierorazio, MD[8]; Ronald S. Boris, MD[9]; Eric A. Singer, MD, MA, MS[10]; Maria I. Carlo, MD[11]; Mary B. Daly, MD, PhD[12]; Elizabeth P. Henske, MD[13]; Colette Hyatt, MS[14]; Lindsay Middleton, RN[4]; Gloria Morris, MD, PhD[1]; Anhyo Jeong, BS[2]; Vivek Narayan, MD, MS[7,15]; W. Kimryn Rathmell, MD, PhD[16]; Ulka Vaishampayan, MD [17]; Bruce H. Lee, MBA[18]; Dena Battle, BS[19]; Michael J. Hall, MD, MS[20]; Khaled Hafez, MD[21]; Michael A. S. Jewett, MD[22]; Christina Karamboulas, PhD[22]; Sumanta K. Pal, MD [23]; A. Ari Hakimi, MD[11]; Alexander Kutikov, MD[20]; Othon Iliopoulos, MD[24]; W. Marston Linehan, MD[3]; Eric Jonasch, MD[25]; Ramaprasad Srinivasan, MD, PhD[3]; and Brian Shuch, MD [2]

[1]Department of Urology, State University of New York (SUNY, Upstate Medical University, Syracuse, New York; [2]Department of Urology, University of California Los Angeles, Los Angeles, California; [3]Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland; [4]Department of Medicine, Division of Hematology-Oncology, University of Texas (UT) Southwestern Medical Center, Dallas, Texas; [5]Department of Surgery, Division of Urology, Howard University Hospital, Washington, District of Columbia; [6]Division of Human Genetics and Translational Medicine, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [7]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [8]Brady Urological Institute and Department of Urology, Johns Hopkins School of Medicine, Baltimore, Maryland; [9]Indiana University School of Medicine, Indianapolis, Indiana; [10]Section of Urologic Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey; [11]Memorial Sloan Kettering Cancer Center, New York, New York; [12]Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, Pennsylvania; [13]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [14]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania; [15]Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [16]Department of Medicine, Vanderbilt University, Nashville, Tennessee; [17]Department of Oncology, Karmanos Cancer Center/Wayne State University, Detroit, Michigan; [18]Driven To Cure, Silver Spring, Maryland; [19]The Kidney Cancer Research Alliance, Leesburg, Virginia; [20]Department of Surgery, Division of Urology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; [21]Department of Urology, University of Michigan, Ann Arbor, Michigan; [22]Division of Urology, Department of Surgery, Princess Margaret Cancer Center, Toronto, Ontario, Canada; [23]Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, California; [24]Massachusetts General Hospital Cancer Center, Boston, Massachusetts; [25]The University of Texas MD Anderson Cancer Center, Houston, Texas

Cancer November 1, 2021

New Additions to Guidelines: AUA and NCCN

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021
Hereditary Renal Cell Carcinomas

NCCN Guidelines Index
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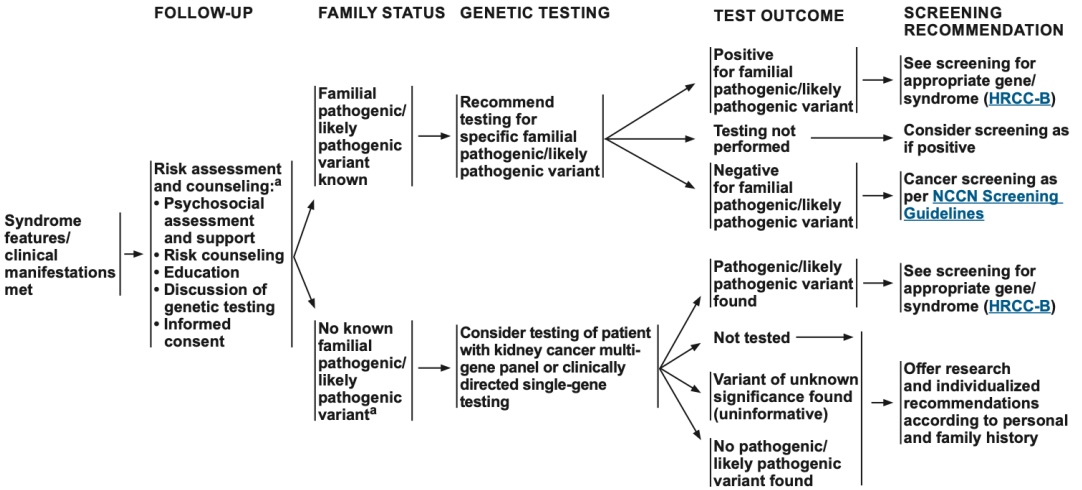
Discussion



[a] In individuals who meet diagnostic criteria, but in whom no germline mutations are identified, consider workup for mosaicism.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GENE-1

Evaluation and Counseling

EVALUATION/DIAGNOSIS

1. Obtain high quality, multiphase, cross-sectional abdominal imaging to optimally characterize/stage the renal mass.
2. Obtain CMP, CBC, and UA. If malignancy suspected, metastatic evaluation should include chest imaging and careful review of abdominal imaging.
3. Assign CKD stage based on GFR and degree of proteinuria.

RENAL MASS BIOPSY (RMB)

1. Counsel regarding rationale, positive/negative predictive values, potential risks and non-diagnostic rates of RMB.
2. RMB should be considered when a mass is suspected to be hematologic, metastatic, inflammatory, or infectious.
3. RMB should be obtained on a utility-based approach, whenever it may influence management. RMB is not required for: a) young/healthy patients who are unwilling to accept the uncertainties associated with RMB; or b) older/frail patients who will be managed conservatively independent of RMB.
4. Multiple core biopsies are preferred over FNA.

COUNSELING

1. A urologist should lead the counseling process and should consider all management strategies. A multidisciplinary team should be included when needed.
2. Counseling should include current perspectives about tumor biology and a patient-specific oncologic risk assessment. For cT1a tumors, the low oncologic risk of many small renal masses should be reviewed.
3. Counseling should review the most common and serious urologic and non-urologic morbidities of each treatment pathway and the importance of patient age, comorbidities/frailty, and life expectancy.
4. Physicians should review the importance of renal functional recovery related to renal mass management, including risk of progressive CKD, potential short/long-term need for dialysis, and long-term overall survival considerations.
5. Consider referral to nephrology in patients with a high risk of CKD progression, including those with GFR < 45[2], confirmed proteinuria, diabetics with preexisting CKD, or whenever GFR is expected to be < 30[2] after intervention.
6. Recommend genetic counseling for all patients ≤ 46 years of age with renal malignancy, those with multifocal or bilateral renal masses, or whenever: 1) the personal or family history suggests a familial RCC syndrome; 2) there is a first-or second-degree relative with a history of renal malignancy or a known clinical or genetic diagnosis of a familial renal neoplastic syndrome (even if kidney cancer has not been observed); or 3) whenever the patient's pathology demonstrates histologic findings suggestive of such a syndrome.

Intervention (PN, RN, or TA)[3] or Active Surveillance (AS)

Changing Management of VHL Disease

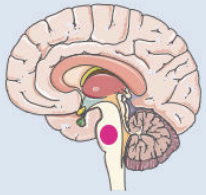
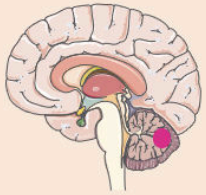
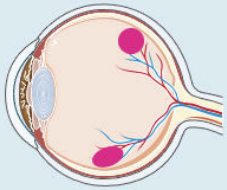
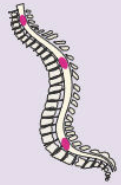
Von Hippel-Lindau

- 1 in 30k individuals; nearly 100% penetrant
- 80-90% with family history of VHL (~10% *de novo* mutation)
- Median survival previously 30-40 but with modern management, improved outcomes (*median survival now 60-65*)
- Highly morbidity with multiple procedures

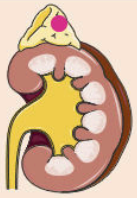
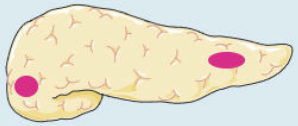
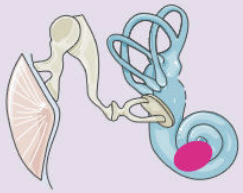
  -many patients unable to work and have permanent neurologic, ocular, and renal functional compromise

Holy Grail is Medical Management

VHL Disease-Associated Hemangioblastomas

Location		Risk/Age	Symptoms
Brainstem		Cumulative incidence: 10%–25% Mean age: 32 years (12–46 years)	• Decreased feeling in the arms, legs and body • Walking difficulties • Swallowing difficulties • Headaches • Poor coordination
Cerebellum		Cumulative incidence: 44%–72% Mean age: 33 (9–78 years)	• Difficulty walking/muscle coordination • Dizziness • Headaches • Double vision • Vomiting • Seizures
Retina		Cumulative incidence: 26%–60% Mean age: 25 years (1–67 years)	• Vision loss • Retinal detachment
Spinal cord		Cumulative incidence: 13%–50% Mean age: 33 years (12–66 years)	• Decreased feeling in the arms, legs and body • Weakness • Difficulty walking • Difficulties with bowel and bladder function

VHL Disease-Associated Tumors

Manifestation		Risk/Age	Symptoms
Renal Cell Carcinoma		Cumulative incidence: 24%–45% Mean age: 37 years (16–67 years)	• Hematuria • Lump/mass on the side or lower back • Pyrexia • Unintentional weight loss • Dull ache/pain: side, abdomen or lower back • Fatigue • Gravity dependent edema
Pheochromocytoma		Cumulative incidence: 10%–20% Mean age: 30 years (5–58 years)	• High blood pressure • Sweating • Headaches • Rapid/irregular heartbeats • Feelings of anxiety/panic • Pale skin • Dizziness, lightheadedness • Tremors • Weight loss
Pancreatic Neuroendocrine Tumor/Cysts		Cumulative incidence: 35%–70% Mean age: 36 years (5–70 years)	• Primarily asymptomatic • Non-functional • Mass effect → bile duct obstruction → Jaundice/icterus • Pain: abdominal or back (uncommon) • Bloating, nausea, vomiting or indigestion (uncommon)
Endolymphatic Sac Tumor		Cumulative incidence: 10% Mean age: 22 years (12–50 years)	• Hearing loss • Tinnitus • Improper balance • Facial Paralysis • Aural fullness

Screening Following VHL Disease Diagnosis

EXAM / TEST → CONDITION DETECTED

Exam or test	Condition screened for
History & physical exam	All VHL-related conditions
Dilated ophthalmic exam	Retinal hemangioblastoma
Blood pressure + plasma/urine metanephrines	Pheochromocytoma
MRI — brain & spine (with/without contrast)	CNS hemangioblastoma
MRI — abdomen (with/without contrast)	Renal cell carcinoma, pheochromocytoma, paraganglioma, pancreatic NET/cyst
Audiological exam + MRI of internal auditory canal	Endolymphatic sac tumor

SCREENING SCHEDULE BY AGE

Ages 1–4 years

- Neurological screening (annual)
- Dilated ophthalmoscopy (annual)
- Physical exam + BP (annual)

Ages 5–15 years

- Neurological screening (annual)
- Dilated ophthalmoscopy (annual)
- Physical exam + BP (annual)
- Lab: (nor)metanephrines (annual)

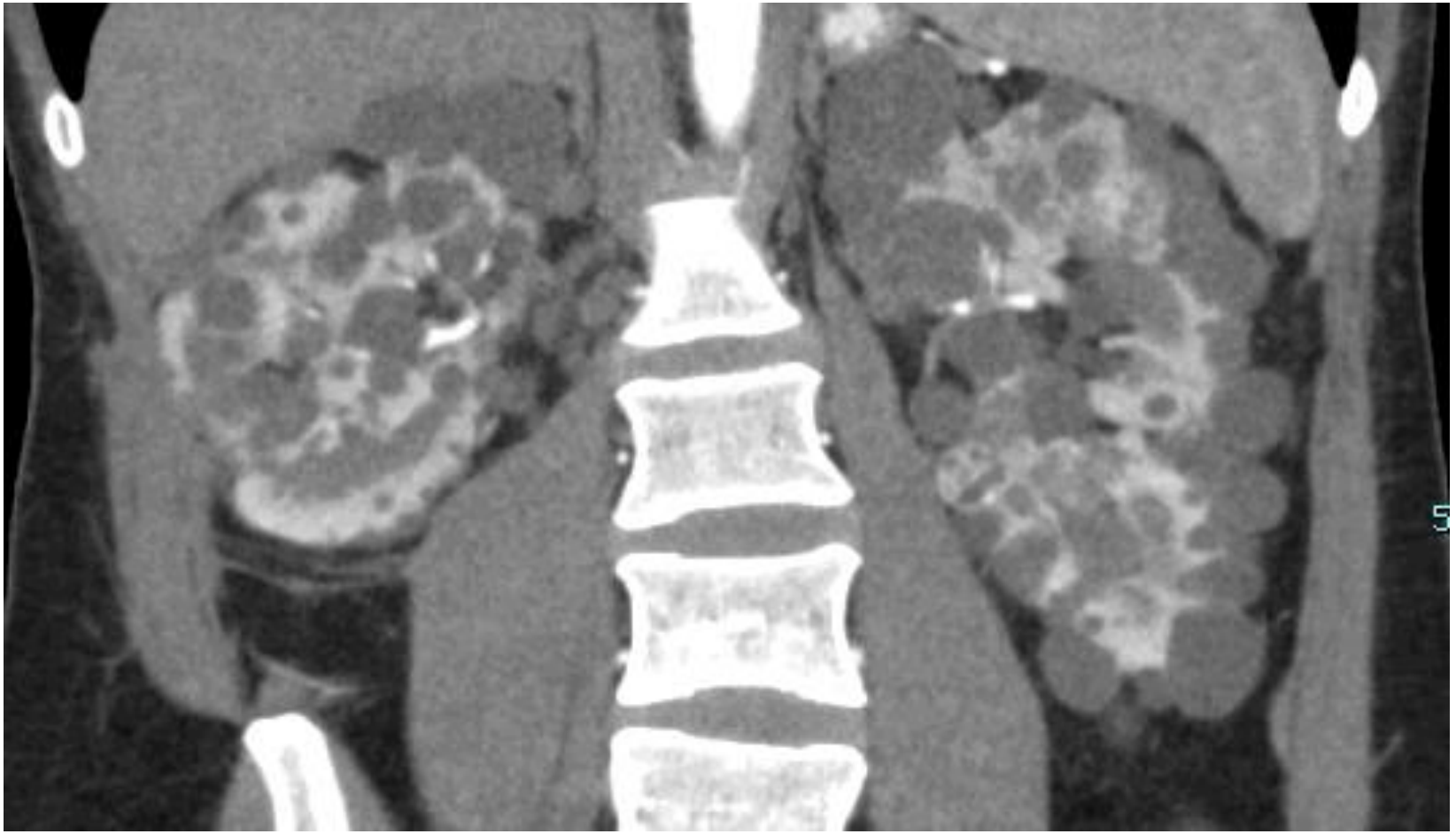
Ages ≥16 years

- Neurological screening (annual)
- Dilated ophthalmoscopy (annual)
- Physical exam + BP (annual)
- Lab: (nor)metanephrines (annual)
- MRI brain + spine (biannual)
- MRI abdomen (annual/biannual)

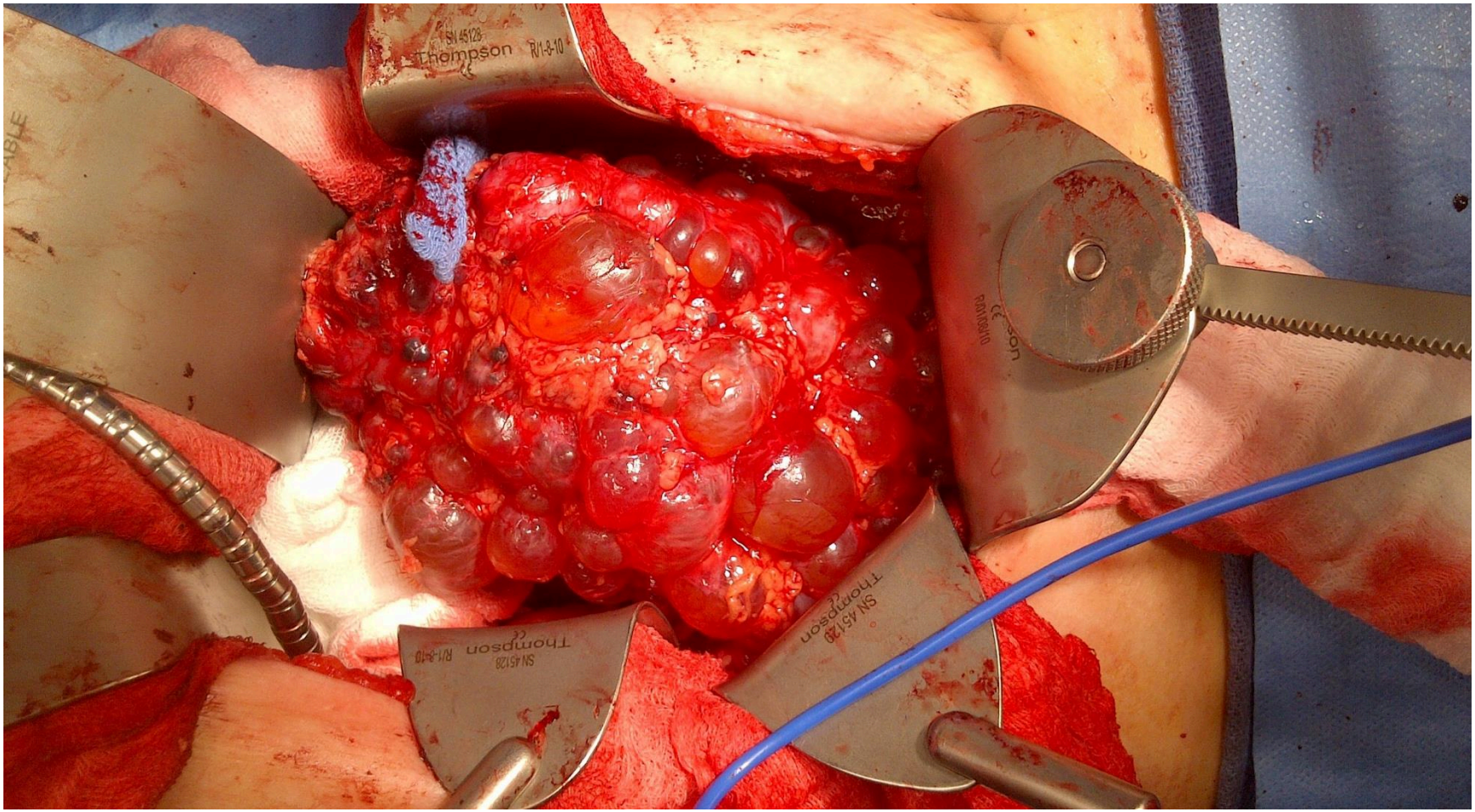
Audiological exam + MRI auditory canal

Frequency determined by clinical findings — add at any age if endolymphatic sac tumor suspected.

VHL Kidneys



Intra-Operative VHL Kidneys

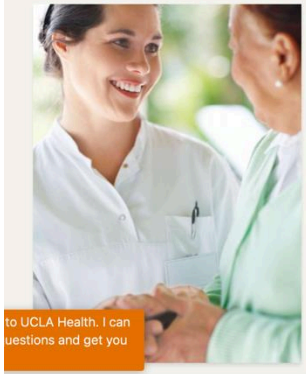


Medical Services

Von Hippel-Lindau Disease

Our expert team leads one of the largest VHL treatment programs in the western United States. You receive comprehensive, multispecialty care.

About Us | What is VHL Disease? | VHL Disease Types | Diagnosing VHL | Monitoring for VHL | Expert Team | Resources



to UCLA Health. I can
uestions and get you

Why choose UCLA Health for VHL disease care?

UCLA Health's Von Hippel-Lindau (VHL) Disease Program is the only VHL clinical care center in Southern California recognized by the VHL Alliance and one of only a few in the western United States. This designation means you receive treatment from a coordinated, multispecialty team of VHL experts that you can trust to provide you with comprehensive care.

Highlights of our program include:

Find your care

Our specialists continually research and bring you the latest effective treatment options. Call 310-794-2858 to learn more about VHL care at UCLA Health.

Find a provider

Request an appointment

Our locations

Helpful Links

UCLA's multidisciplinary program transforms the outlook for people with von Hippel-Lindau disease

Experts from multiple specialties collaborate to provide comprehensive care for rare disease.

The VHL program brings together a multidisciplinary team of experts, including Dr. Michael Gorin, professor of ophthalmology and human genetics; Dr. Brian Shuch, professor of urology; and Dr. Isaac Yang, professor of neurosurgery.

November 25, 2024
By Denise Heady, MA
6 min read

Hollie Williamson was a sophomore in high school when doctors discovered she had a brain tumor — the first of many tumors Williamson would have to deal with throughout her life.

While it was upsetting news to hear, it wasn't a complete shock to Williamson or her family. Her mother had been diagnosed with von Hippel-Lindau disease (VHL), a rare genetic disorder that significantly increases the risk of tumors in specific areas of the body such as the eyes, spine, brain and internal organs. A person with a parent with VHL has a 50% chance of inheriting the disease.

"When I found out I had a brain tumor, we all knew it was VHL," Williamson,

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Cancer Center Members

Brian Shuch, MD
Urology

Isaac Yang, MD
Neurological Surgery

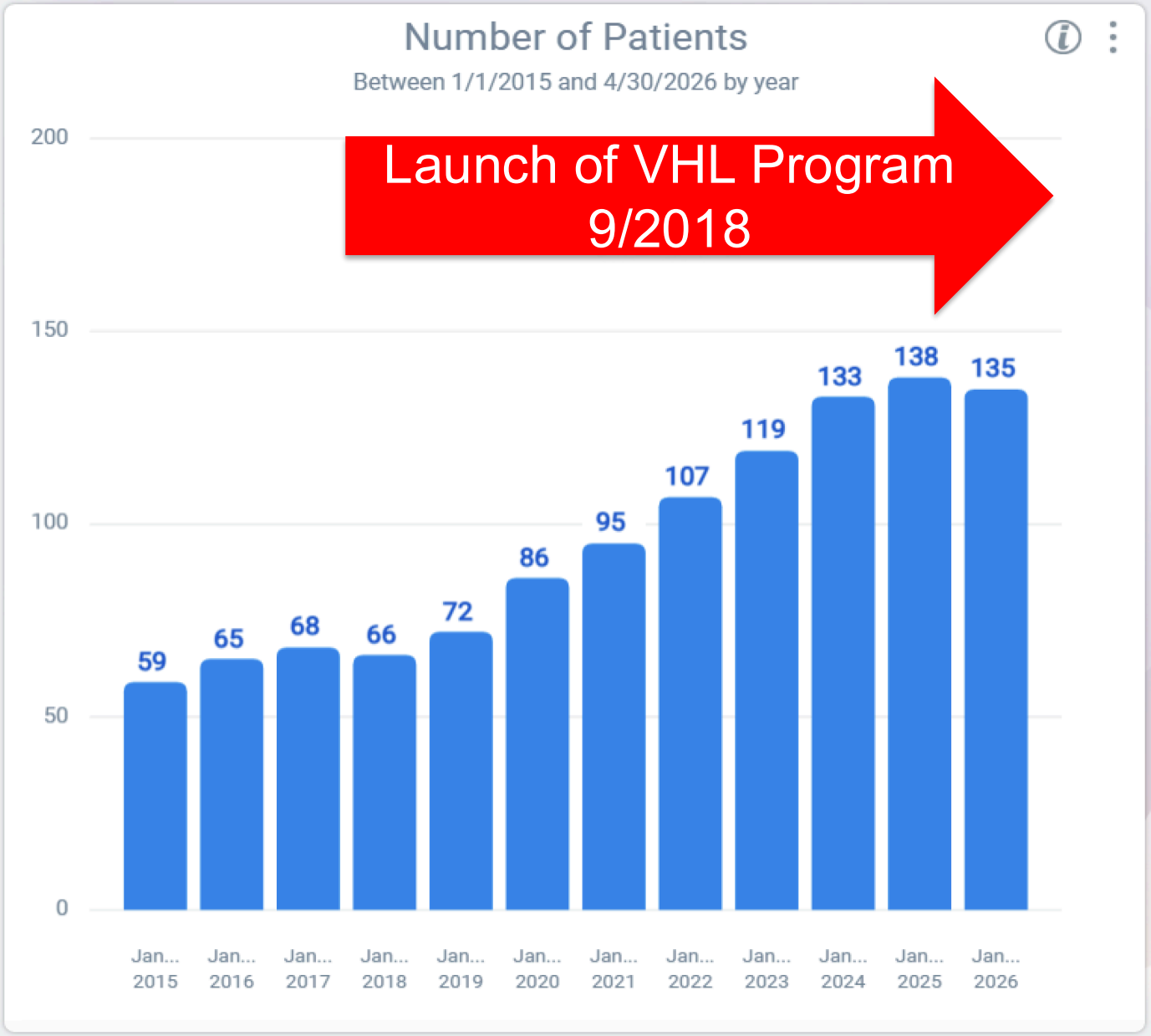
VHL Clinical Care Centers

- There are only a few VHL Clinical Centers on the West Coast of the US that are committed to providing state of the art, coordinated care for patients with VHL disease.
- These specialized centers, have experts with clinical and research interest in the unique aspects of VHL care
- Systems are already established to coordinate multidisciplinary are across a team of specialist with extensive knowledge about VHL disease

David Geffen School of Medicine

Cogito ergo sum SlicerDicer

Undo Redo



Population

Base: All Patients
Diagnosis: Von Hippel-Lindau syndrome

Slices

No Slices

Measures

Number of Patients

Dates

Start Date:	Jan 1, 2015
End Date:	Apr 30, 2026
Slice By:	Year
Compare By:	None

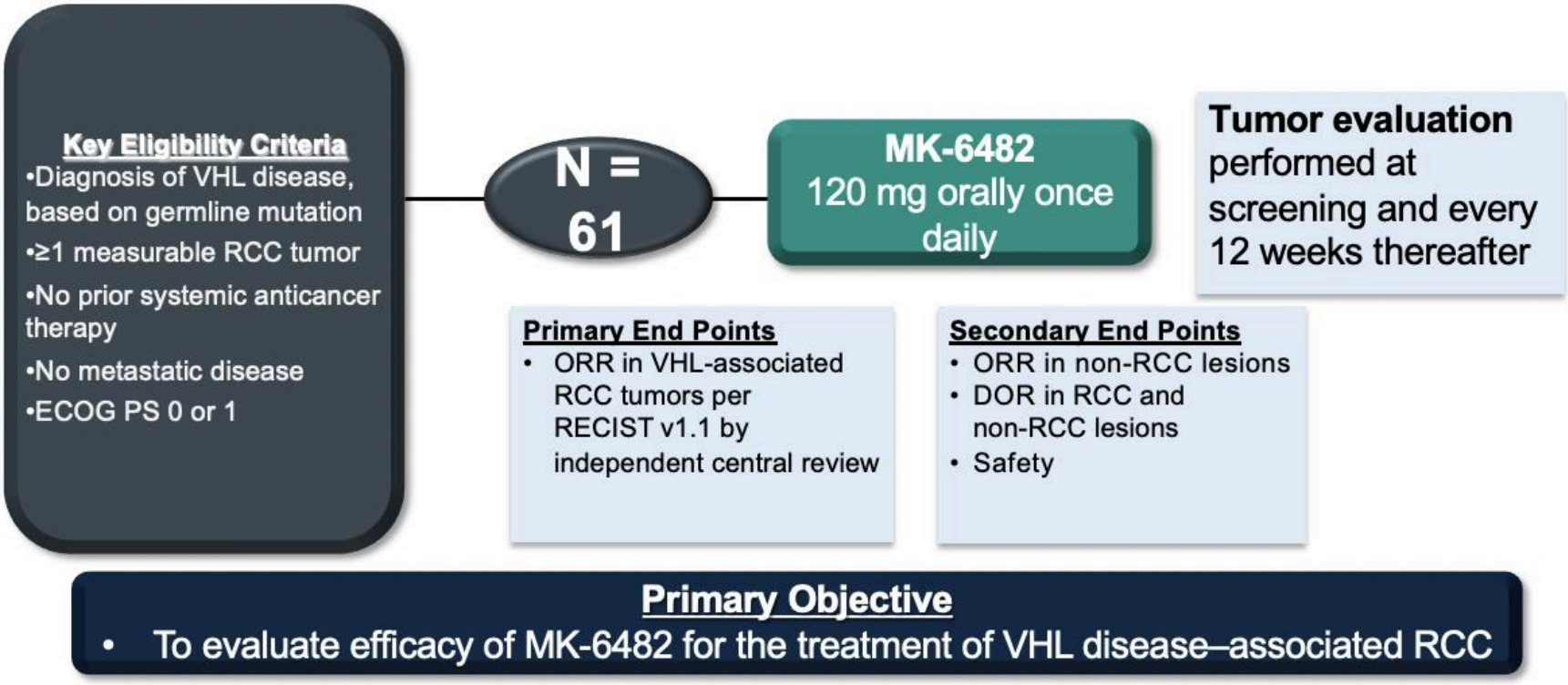
Visual Options

Graph Type:

Bar Co

LA and OC the #1 and #3 VHL counties in the US

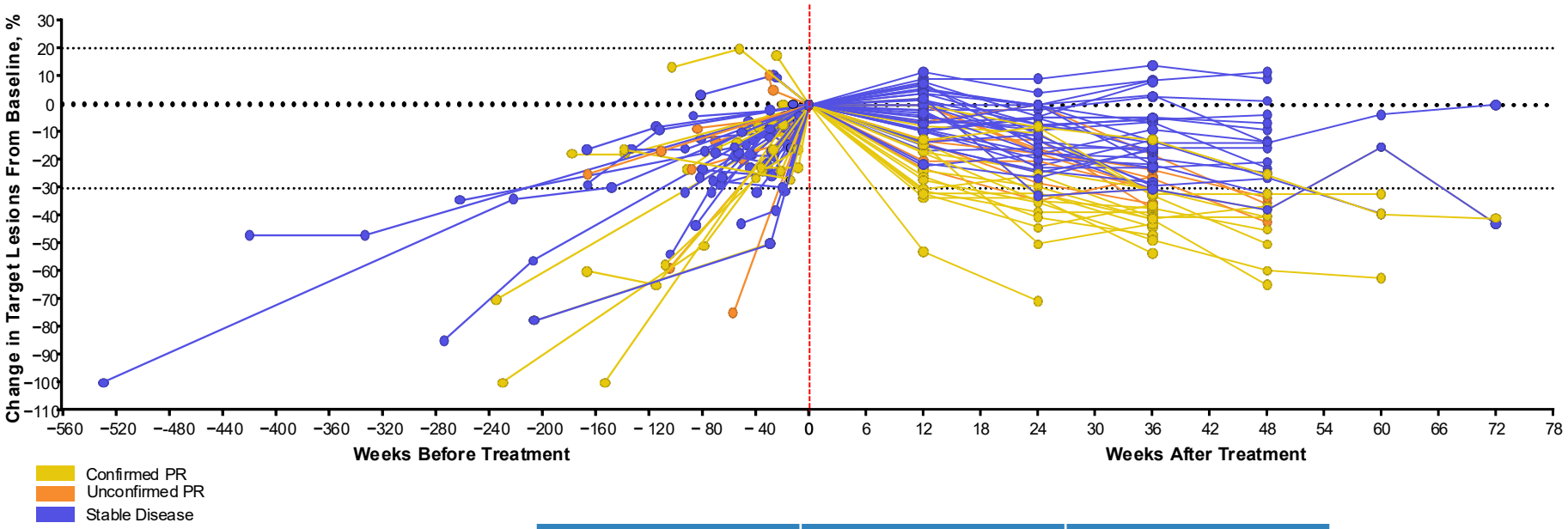
Phase 2 Study: MK-6482 for VHL-Associated RCC (NCT03401788)



Target RCC Lesions: Median Linear Growth

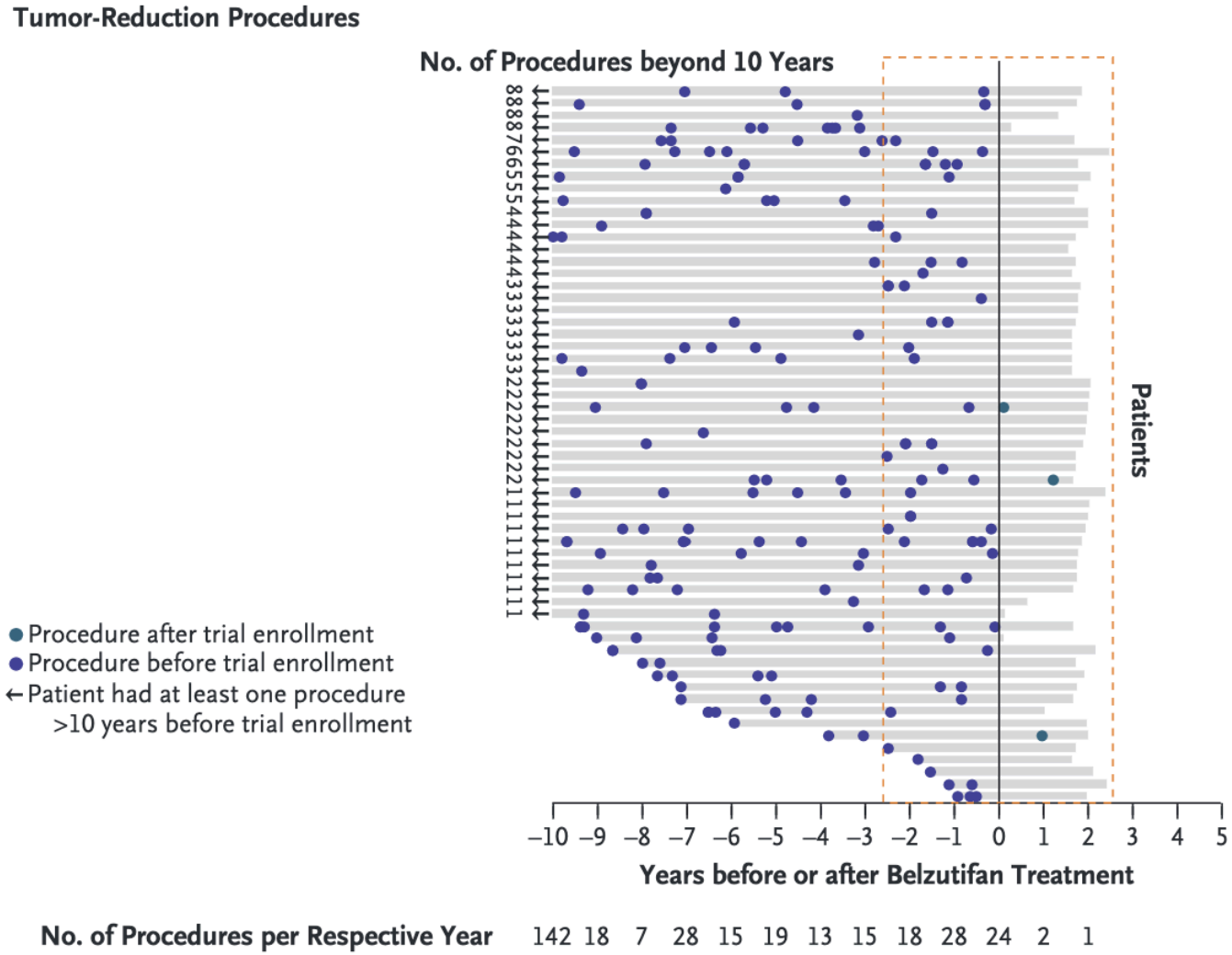
+3.63 mm/year (range, 3.06-10.91) before treatment

-6.40 mm/year (range 23.32-4.48) after treatment



Updated Series:

Tumor Type	Response	CR
RCC	59%	3%
Panc NET	90%	16.6%
CNS HB	38%	15.7%


Tumor-Reduction Procedures
No. of Procedures beyond 10 Years
8888766555444443333333222222211111111111
Patients
Procedure after trial enrollment
Procedure before trial enrollment
←Patient had at least one procedure >10 years before trial enrollment
–10 –9 –8 –7 –6 –5 –4 –3 –2 –1 0 1 2 3 4 5
Years before or after Belzutifan Treatment
No. of Procedures per Respective Year 142 18 7 28 15 19 13 15 18 28 24 2 1

Tolerability & Adverse Events (AEs)

- Belzutifan well-tolerated with G3+ AE in 9.8%
  -Treatment interrupted in 43%
  -Dose reduced in 15% due to AEs

- On-Target effect on EPO leads to Anemia in 53/61 (87%)
  -3.3% (2/61) with G3 anemia
  -on trial ESA used but transfusion now recommended

- Fatigue 57.4% but grade 3 only 4.9%

- Hypoxia seen likely on target effect (2%)
  -Higher frequency in metastatic trials

Jonasch, E. *et al.* Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease. *New Engl J Med* **385**, 2036–2046 (2021).

FDA Grants New Designations to MK-6482 in RCC and VHL Disease

July 29, 2020
Nichole Tucker

Approved August 2021

The FDA has granted a Breakthrough Therapy designation to MK-6482, a novel HIF-2a inhibitor, as treatment of patients with von Hippel-Lindau disease-associated renal cell carcinoma who have non-metastatic tumors that measure less than 3 centimeters in size, unless immediate surgery is needed. The FDA has also granted an Orphan Drug designation to MK-6482 for the treatment of VHL disease alone.

The FDA has granted a Breakthrough Therapy designation to MK-6482, a novel HIF-2alpha inhibitor, as treatment of patients with von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC) who have non-metastatic tumors that measure less than 3 centimeters in size, unless immediate surgery is needed. The FDA has also granted an Orphan Drug designation to MK-6482 for the treatment of VHL disease alone.[1]

The 2 designations were announced in a press release from drug developer, Merck.

“These designations for MK-6482 support the potential of targeting HIF-2α in certain patients with VHL disease, who currently have limited treatment options and face an increased risk for benign tumors as well as several types of cancer,

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 39 (2021) 277–280

UROLOGIC ONCOLOGY

News and Topics

HIF2 Inhibition for von-Hippel Lindau Associated Kidney Cancer: Will Urology Lead or Follow?

Brian Shuch, MD*

Department of Urology, David Geffen School of Medicine, University of California, Los Angeles

Received 13 August 2020; accepted 16 January 2021

Keywords: VHL; RCC; HIF2

Trial involved urologists, medical oncologists, medical geneticists, endocrinologist, and neurologists

Drug can be given across specialties by VHL experts

Post-Test Questions

- Which of the following patients would NOT be automatically referred for genetic counseling/testing and require additional suspicion

A. A 72 year old man with a 3 cm pre-aortic paraganglioma

B. A 31 year old man with a 5 cm pheochromocytoma

C. A 4 year old girl with a 5.2 cm adrenocortical carcinoma

D. A 48 year old female with an 5 cm chromophobe RCC

Pre-Test Questions

- A 32-year-old woman is diagnosed with adrenocortical carcinoma (ACC). She has no significant family history of cancer. According to current guidelines, which is the next step regarding genetic evaluation?

- A. Test only for TP53 because it is the most common hereditary cause of ACC
- **B. Recommend comprehensive germline testing, including TP53 and Lynch syndrome genes**
- C. Genetic testing is only indicated for pediatric patients with ACC
- D. No genetic testing is needed unless a first-degree relative has ACC

Pre-Test Questions

- A 27-year-old man with confirmed VHL disease is found with a new, asymptomatic 3.2 cm pheochromocytoma. He asks whether belzutifan could be used instead of surgery, noting that HIF-2α inhibitors are approved for metastatic pheochromocytoma. Which of the following is the most accurate recommendation?

- A. Belzutifan is appropriate as it can be used for any VHL tumor
- B. Belzutifan may delay surgery for adrenal masses but should only be used after biochemical testing
- C. Belzutifan is preferred over adrenalectomy for localized VHL pheochromocytoma
  D**. Belzutifan is not indicated for adrenal tumors in VHL and should not be used for suspected pheochromocytoma**

bshuch@mednet.ucla.edu

David Geffen School of Medicine | UCLA Health

@kidneycancerdoc

Genetics and Genomics of Prostate Cancer

A practical guide to who, what, and how to test

Hong Truong, MD
Urology Service, Department of Surgery
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering
Cancer Center

Disclosure statement

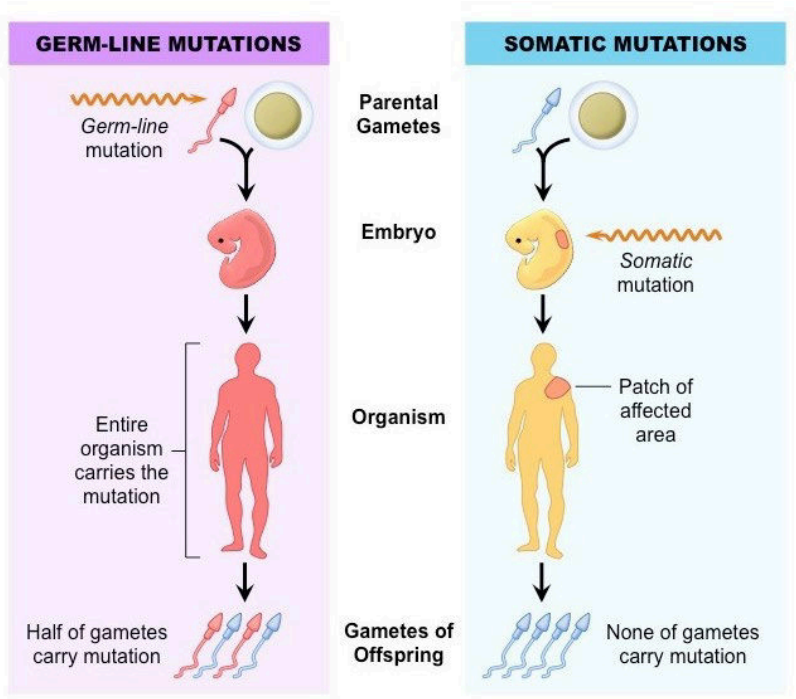
No relevant relationships to disclose

Overview and Objectives

- Which patients with prostate cancer should undergo **genomic profiling**?
- Which patients with prostate cancer should undergo **germline genetic testing**?
- How should we **screen for prostate cancer** in patients with germline alteration?
- How should we **treat prostate cancer** in patients with germline alteration?

How are germline and somatic alterations different?

	Germline mutation	Somatic mutation
Origin	Inherited from a parent De novo	Arise within the cancer
Hereditary	Yes	No
Cells in which the mutation is present	All nucleated diploid cells in the body	Some or all cancer cells
Tissue used for testing	Lymphocyte (blood) Buccal cells (saliva, buccal swab)	Cancer tissue (primary or metastatic)
Predict risk of cancer development	Yes	No
Guide treatment	Yes	Yes
Define cancer prognosis	Yes	Yes



Source: ib.bioninja.com.au

Clinical genomic/genetic tests

Germline genetic testing
Blood/saliva

Tumor genomic profiling
Tumor tissue

Inherited cancer syndromes
(Ex: Invitae, Myriad, GeneDx, Color, etc.)

- Mutation in cancer susceptibility genes
- Treatment consideration
  - PARP inhibitor
  - Immunotherapy
  - Clinical trials
- Cancer screening and prevention
- Cascade testing for at-risk family members

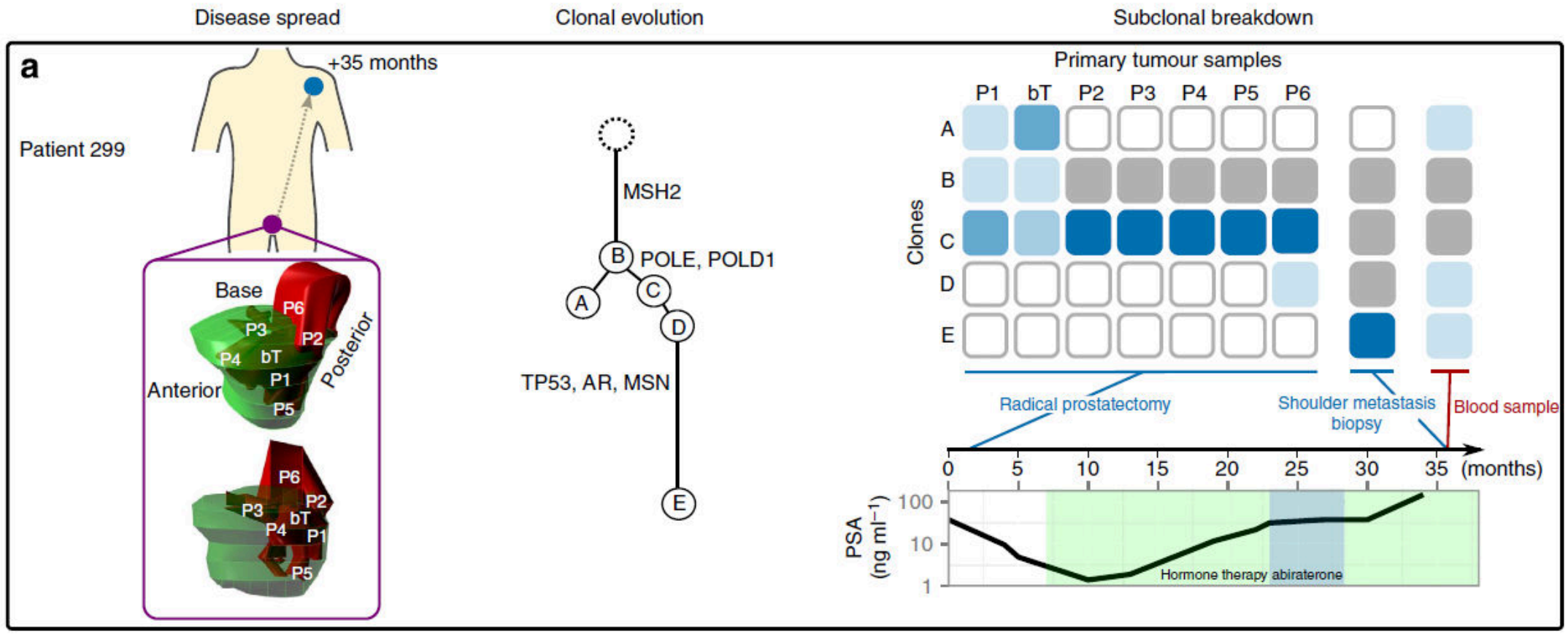
Tumor sequencing:
(Ex: Foundation Medicine, Caris)

- Tumor profiling
  - Microsatellite instability ☆
  - Tumor mutation burden
  - Mismatch repair ☆ deficiency
- Treatment consideration
  - PARP inhibitor
  - Immunotherapy
  - Clinical trials
- Mutations in cancer ☆ susceptibility genes may be somatic or germline in origin

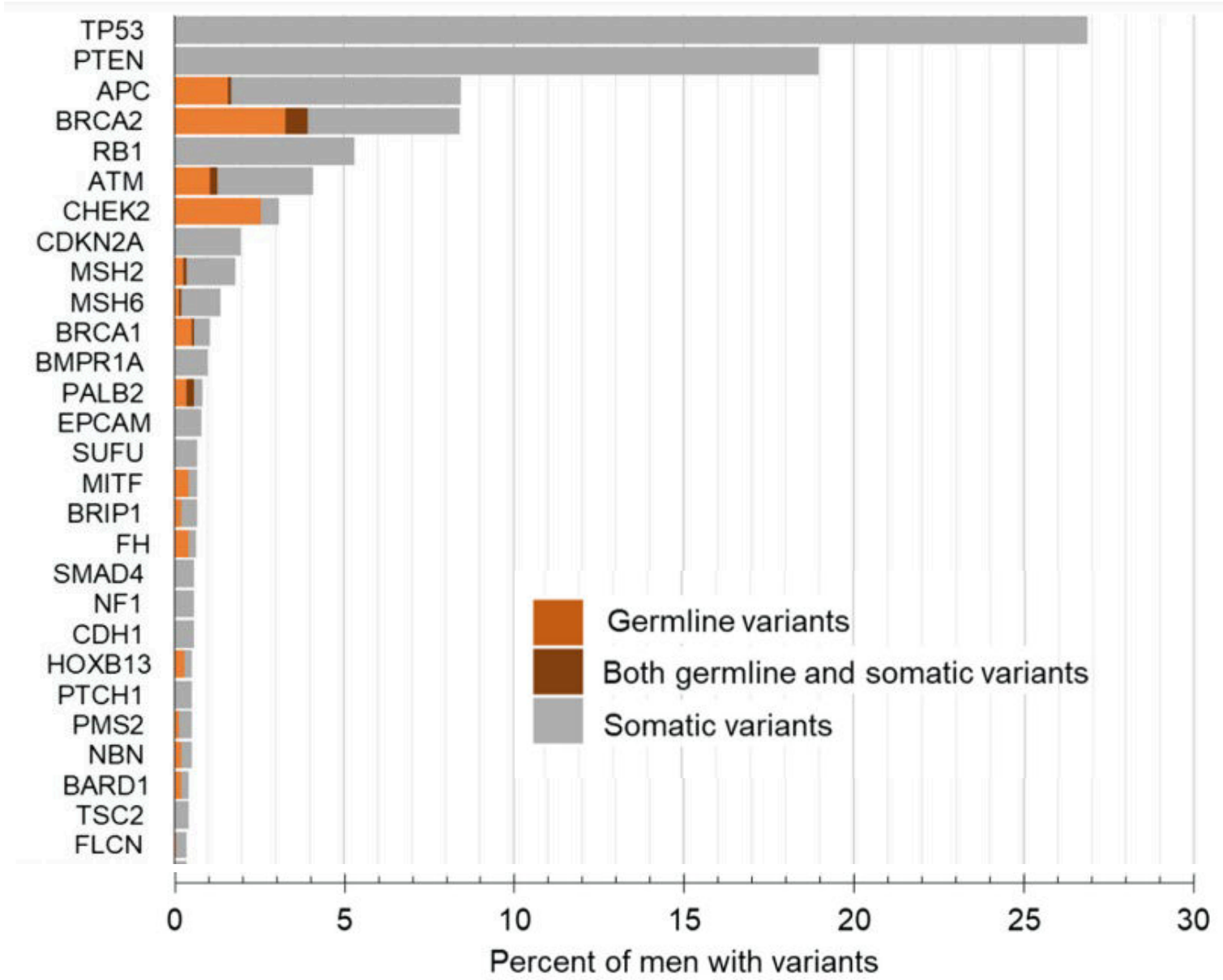
Gene expression analysis
(Ex: Decipher, Prolaris, OncotypeDx, etc)

- Risk stratification for clinically localized disease
- Prognostic biomarkers for
  - Distant metastasis
  - Prostate cancer specific mortality
  - Adverse pathology

Tumor heterogeneity



Distribution of germline & somatic alterations in prostate cancer



Question:

A 70-years old man with metastatic prostate cancer had tumor sequencing of his metastatic retroperitoneal lymph node. The test report shows a *BRCA2* Y1894* pathogenic variant. Without knowing more, which is the best description of this variant?

A. This is a germline mutation.

B. This is a somatic mutation.

C. This mutation may be germline or somatic in origin.

D. This mutation is both germline and somatic since it is found in the metastatic lesion.

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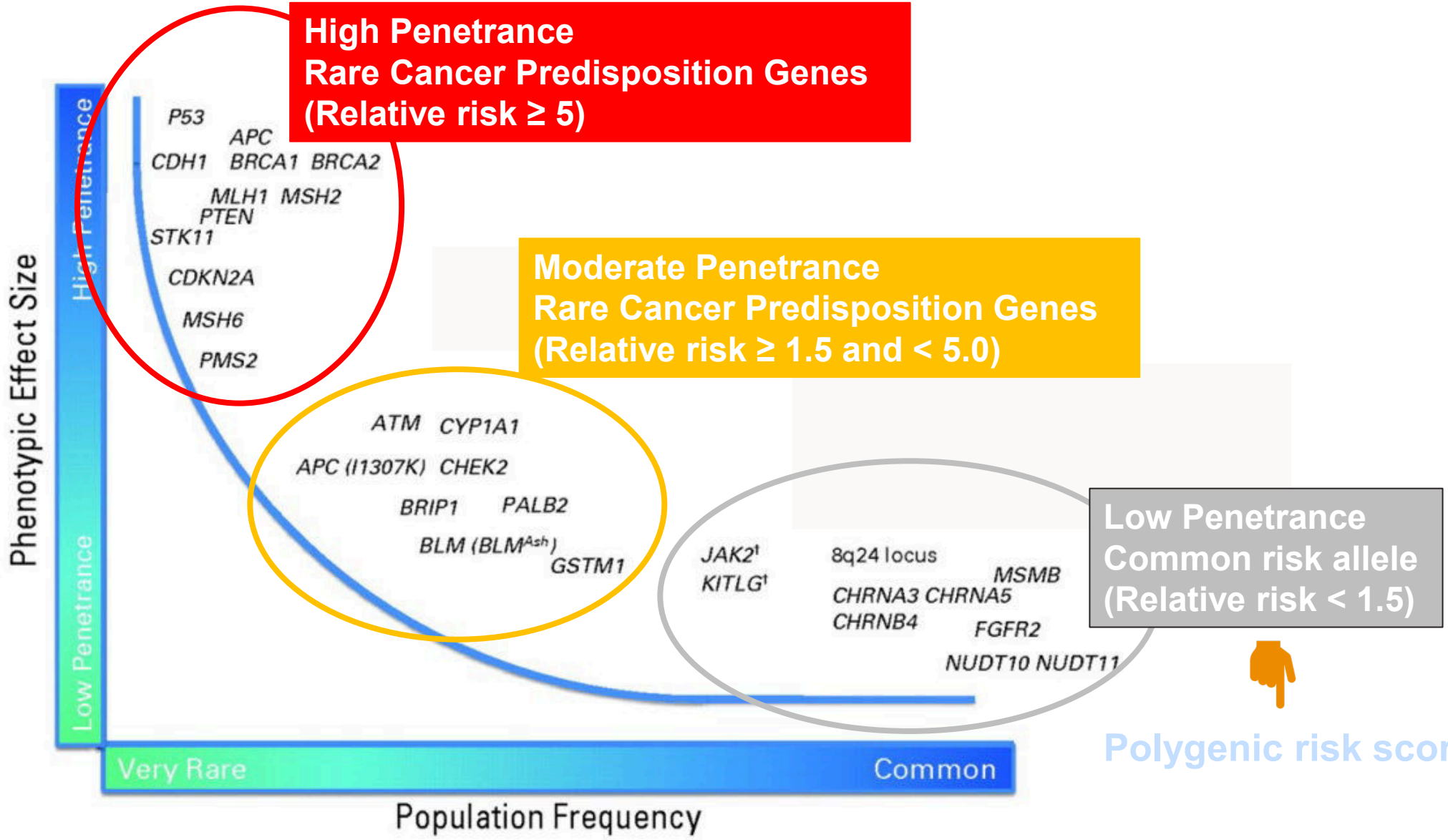
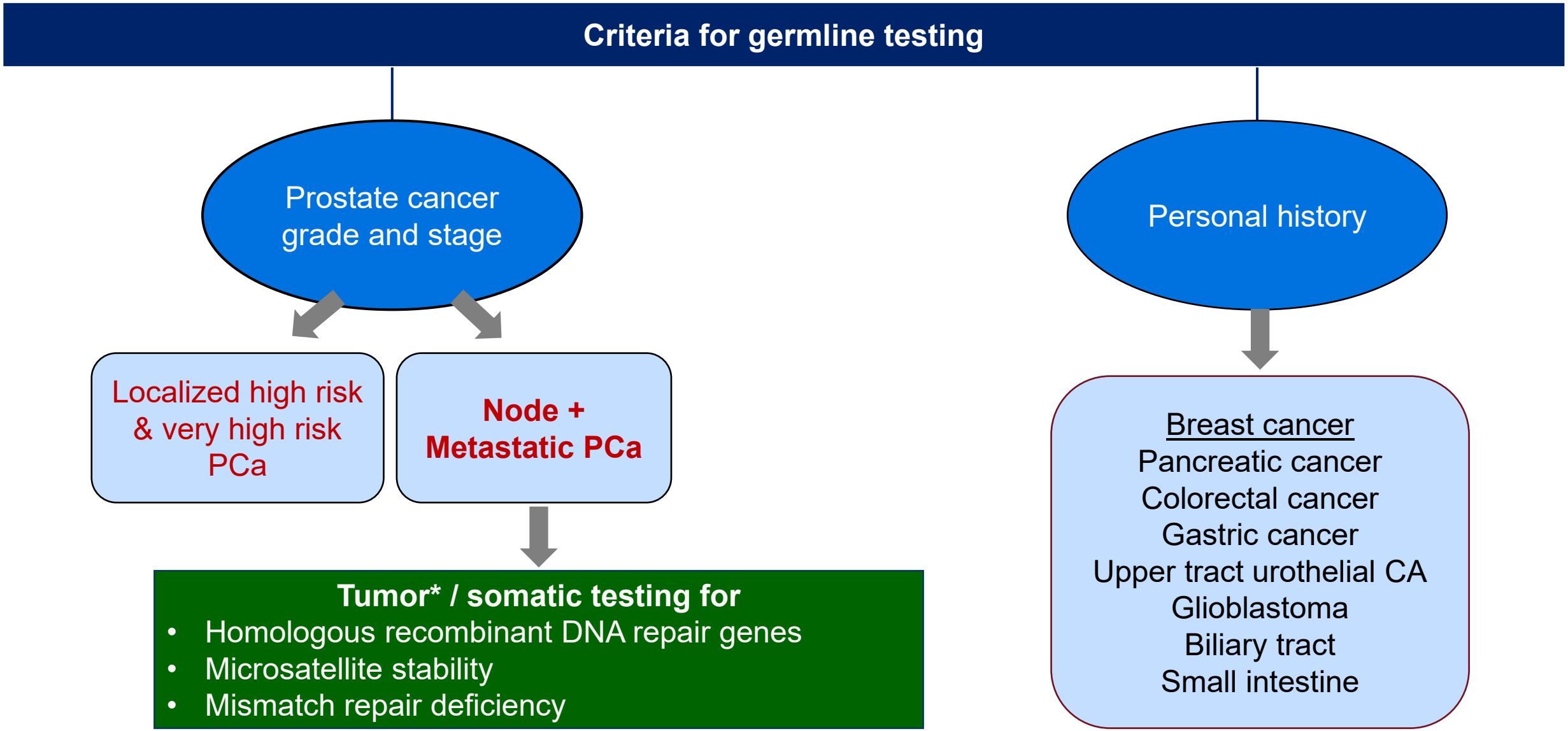
Cancer susceptibility allele



Who should undergo genomic testing



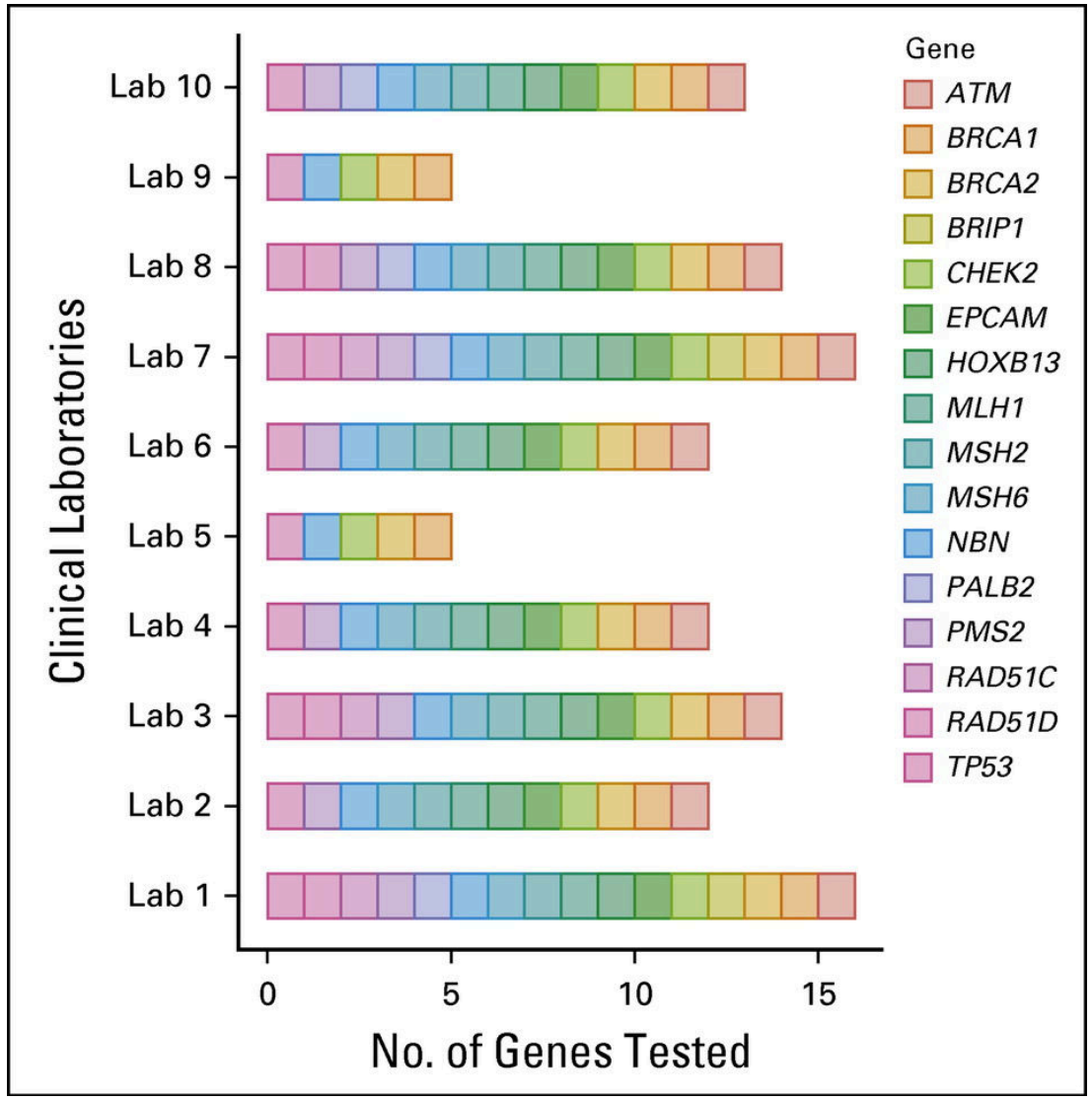
Localized high risk PCa

High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5

Family history criteria

- Ashkenazi Jewish ancestry
- Known family history of familial cancer risk mutation
  - Especially *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMSH2*
- Father or brother or multiple family members with prostate cancer
  - Diagnosed < 60 years
  - Regional / metastatic / or died of prostate cancer
- ≥ 3 cancers on the same side of family, especially diagnosed <50 years
  - Breast, colorectal, endometrial, gastric, bile duct, upper tract urothelial cancer, melanoma, ovarian, pancreatic, small bowel, prostate cancers

What genetic test to order



Germline multigene testing should include BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2

*Additional genes based on clinical context

Prevalence of germline mutation

	Exome Aggregation Cohort General Population ī = 53,105 (%)	Lee et al.[58] Localized Prostate Cancer *ī = 1174 European population (%)	TGCA cohort Localized Prostate Cancer ī = 499 (%)	Leongamornlert et al.[59] Familial Prostate Cancer ī = 191 (%)	Prichard et al.[56] Metastatic Prostate Cancer ī = 692 (%)	Castro et al. Prorepair-B[46] Metastatic CR Prostate Cancer ī = 419 (%)	Nicolosi et al.[62] Invitae Prostate Cancer** ī= 3607 (%)
All Genes: % +ve	2.7%	4.0%	4.6%	7.3%	11.8%	16.2%	17.2%
BRCA1	0.22	0.77	0.60	0.52	0.87	1.0	1.25
BRCA2	0.29	1.0	0.20	2.10	5.35	6.2	4.74
ATM	0.25	0.51	1.0	1.04	1.59	1.9	2.03
PALB2	0.12	0.17	0.40	0.52	0.43	–	0.56
CHEK2	0.61	0.34	0.40	1.04	1.87	0.24	2.88
MLH1	0.02	0.0	0	–	0	–	0.06
MSH2	0.04	0.17	0.20	–	0.14	0.24	0.69
PMS2	0.11	0.09	0.20	0.52	0.29	–	0.54
MSH6	0.08	0.09	0.20	–	0.14	–	0.45
HOXB13	–	–	–	–	–	–	1.12
RAD51D	0.08	0.0	0.20	–	0.43	–	0.15

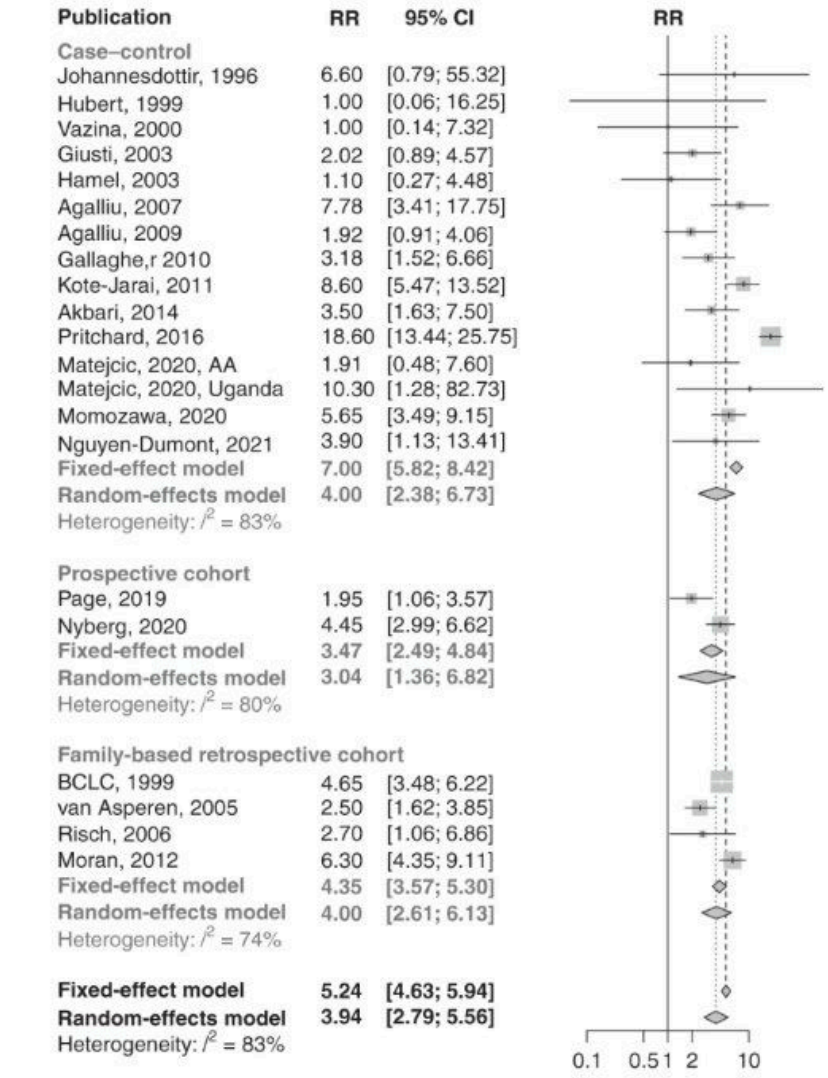
More aggressive prostate cancers are associated with higher risk of having a germline mutation

Prostate cancer stage	Proportion with pathogenic germline variant
No cancer diagnosis	2.7%
Low/intermediate risk localized	4 – 5%
High risk localized	5 – 9%
Metastatic	12 – 17%

Hereditary prostate cancer characteristics

- Higher risk of PCa
  - BRCA1 carrier: 3.8-fold
  - BRCA2 carrier: 8.6-fold
- Early onset
- Aggressive phenotype
  - Higher Gleason grade ≥ 8
  - More advanced disease (T3/4, N+, M+)
- Worse outcome
  - Lower cancer specific survival

Fig. 3: Forest plots of overall *BRCA2* RR estimates.



How to screen for PCa in patients with germline alterations

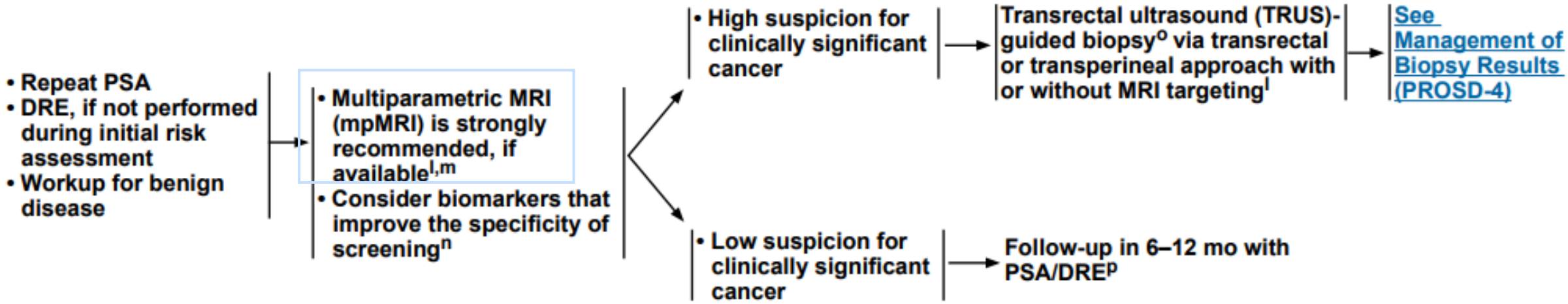
For men with personal history of pathogenic variants in prostate-cancer associated risk genes, such as *BRCA2*

- Begin screening at age 40
- Annual PSA and DRE
  - "Normal" serum PSA range
    - Age 40 – 49: 0 – 2.5
    - Age 50 – 59: 0 – 4.0
    - Age 60 – 69: 0 – 4.5
    - Age 70 – 79: 0 – 5.5
- Stop screening at age 75 unless patient is very healthy with little comorbidities

PSA cutoff > 3 ng/ml for BRCA1/2 carrier

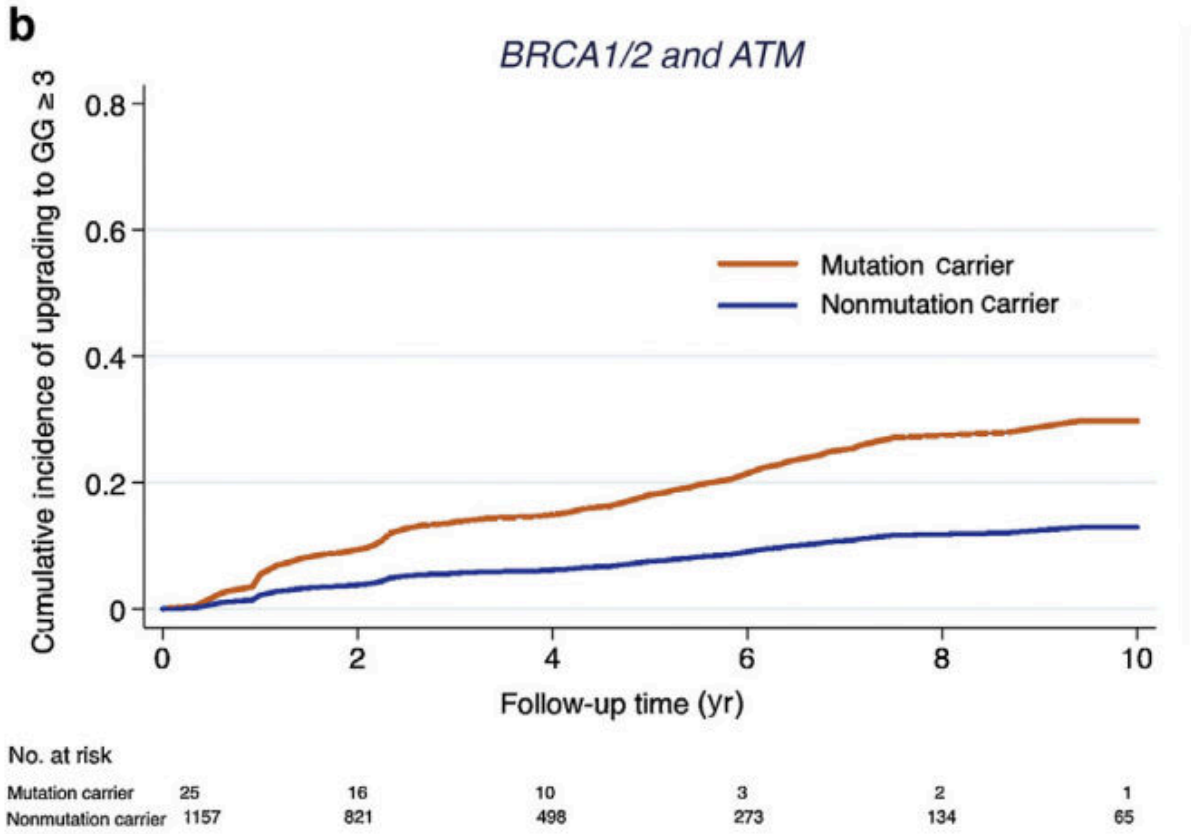
Prostate-cancer associated risk genes
BRCA2
BRCA1
ATM
CHEK2
PALB2
HOXB13
MLH1
MSH2
MSH6
PMS2
TP53

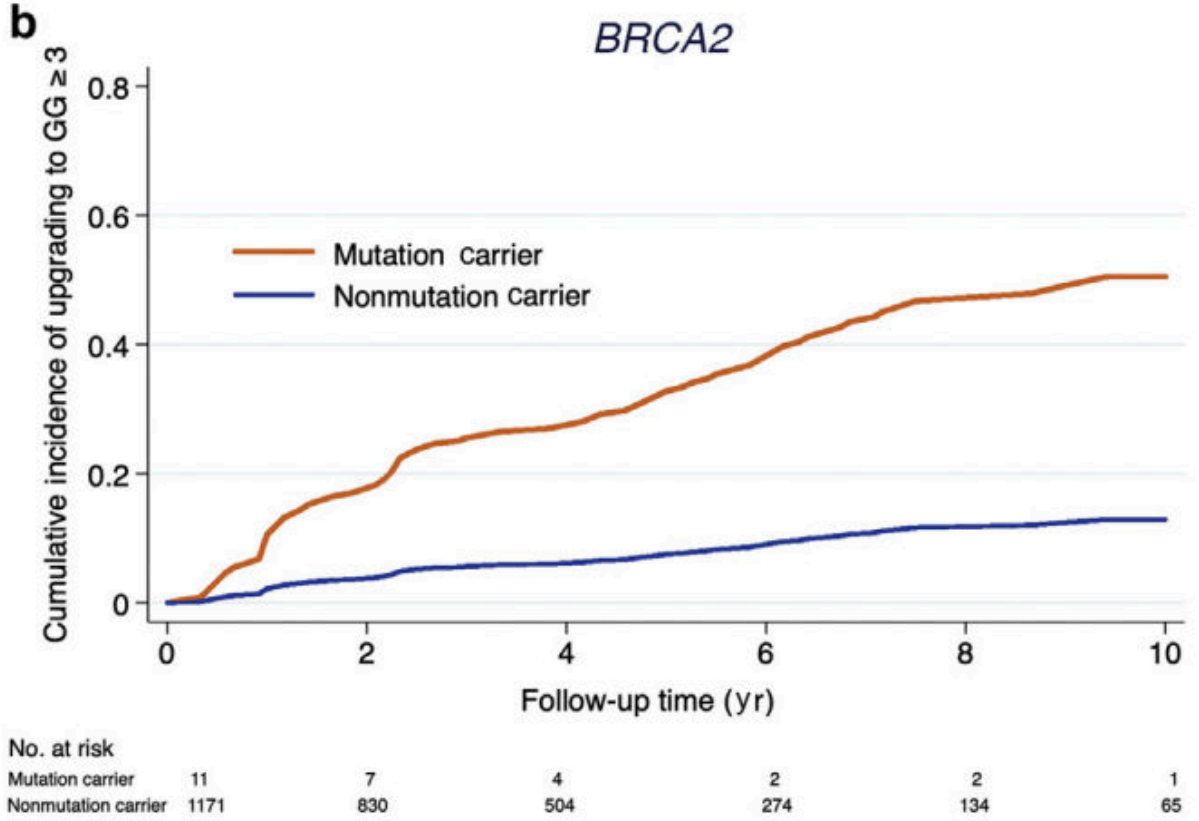
How to screen for PCa in patients with germline alterations



How to treat localized PCa in patients with germline alterations

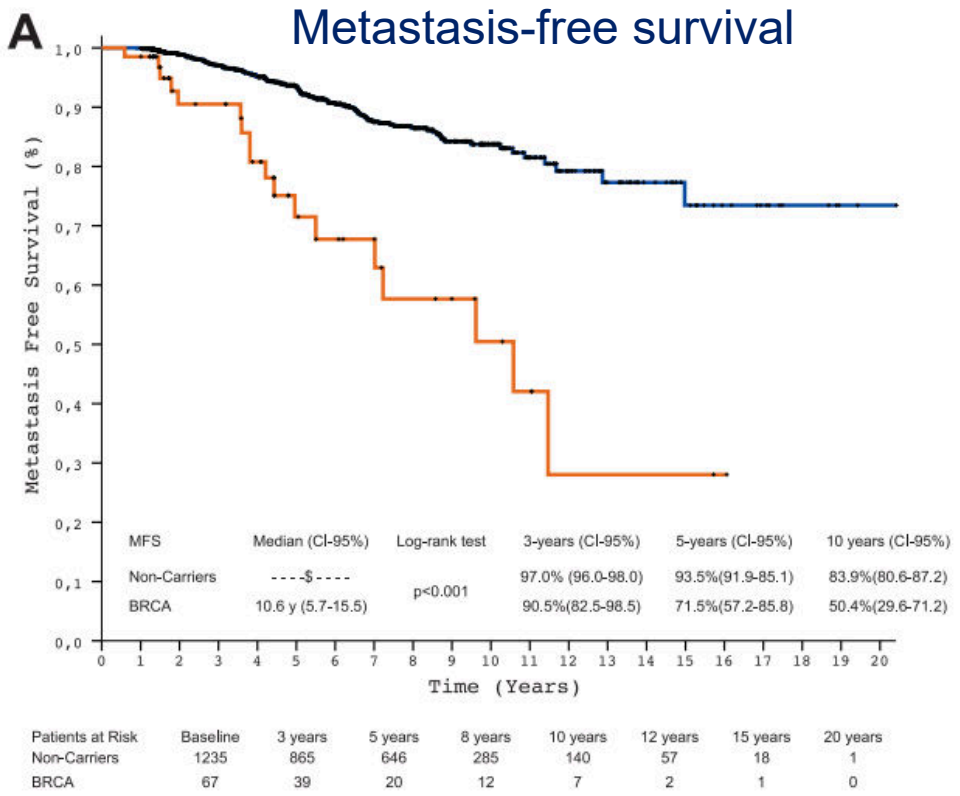
- Active surveillance: higher likelihood of grade reclassification in men with *BRCA1/2* or *ATM*

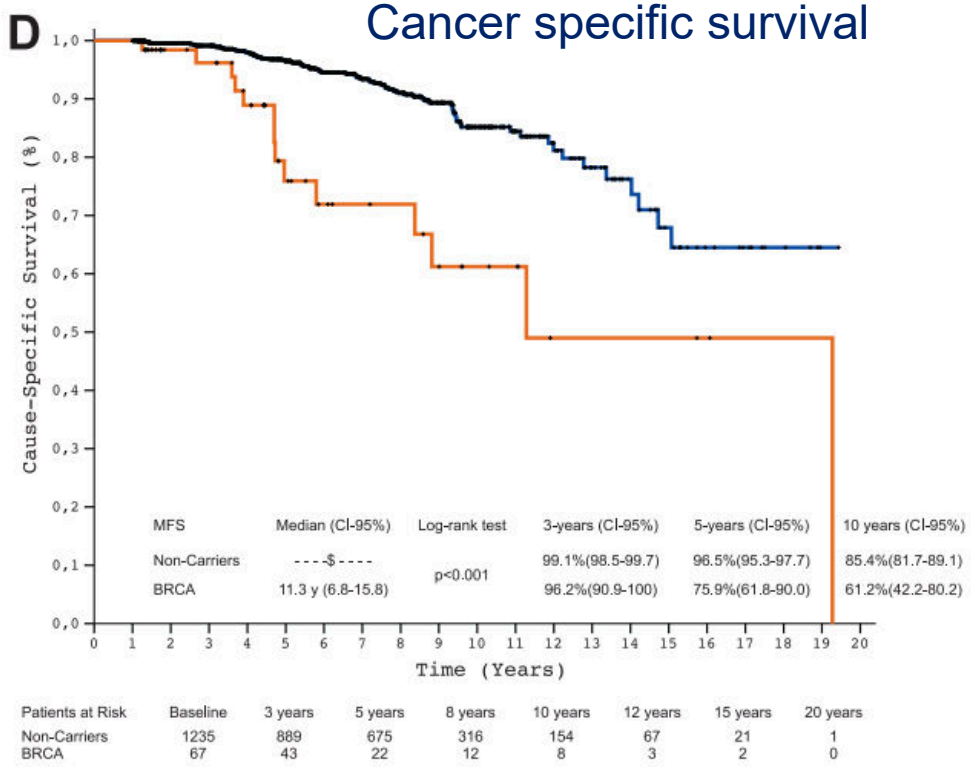




How to treat localized PCa in patients with germline alterations

- Definitive treatment with surgery or radiation in men with *BRCA* mutation
  - Worse metastasis-free survival (HR 2.36, CI 1.38 – 4.03)
  - Worse cancer specific survival (HR 2.17, CI 1.16 – 4.07)

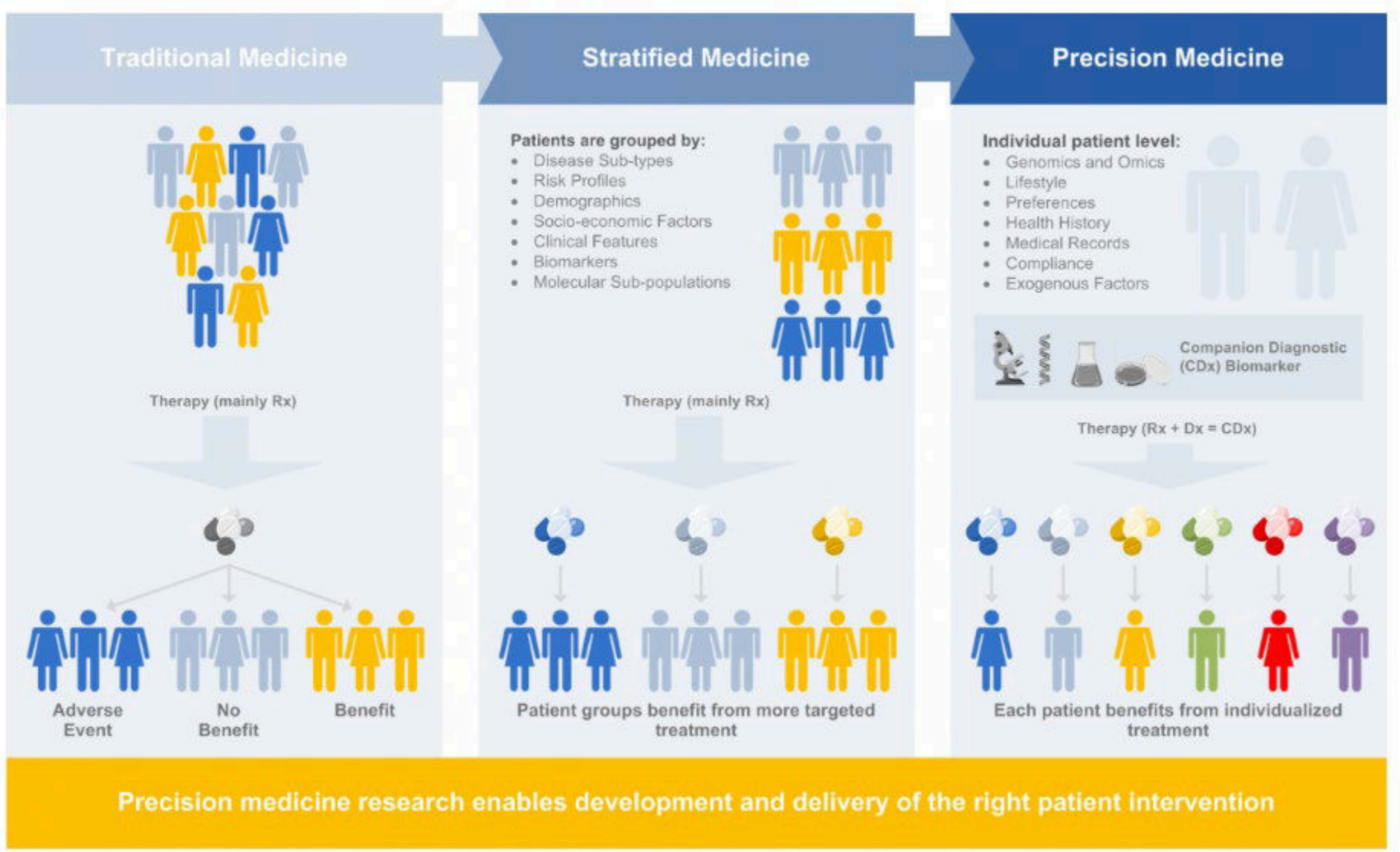




How to treat localized PCa in patients with germline alterations

- Currently no guideline recommendation for management of localized prostate cancer in men with *BRCA* mutation
- Close follow up in setting of active surveillance or definitive treatment
- The role of germline testing in management of men with localized prostate cancer is unclear
  - Low prevalence of germline mutation
  - Unclear management strategy in germline carriers

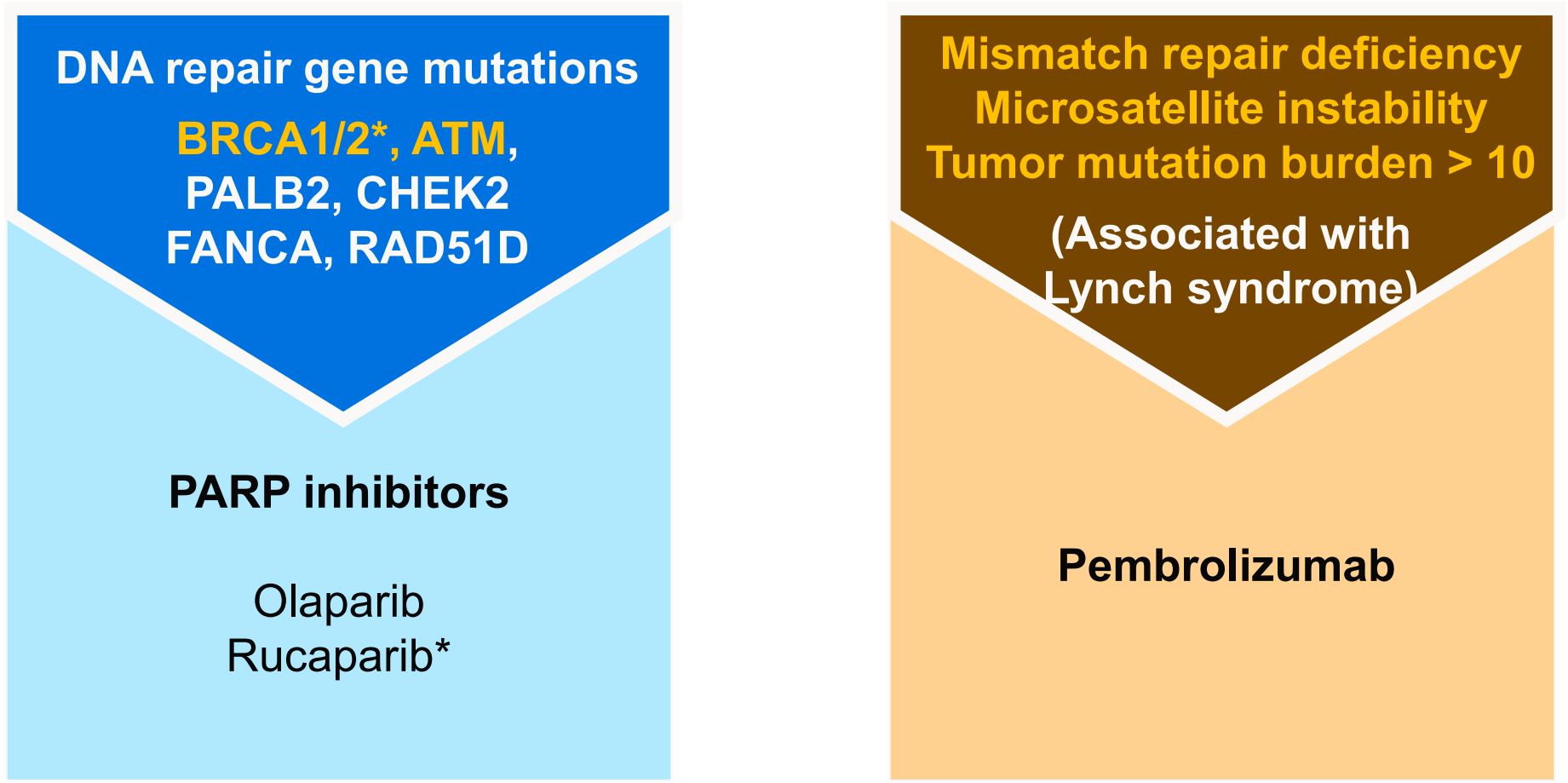
How to treat advanced PCa in patients with germline alterations



Source: Forbes & Linguamatics.com

How to treat advanced PCa in patients with germline alterations

Metastatic castration resistant prostate cancer



Conclusion

- Genetic and genomic profiling is the standard of care in the management of patients with prostate cancer.
- Most important prostate-cancer susceptibility genes: BRCA2, BRCA1, PALB2, HOXB13, ATM, CHEK2
- Patients across the spectrum of prostate cancer qualify for genetic evaluation with implications for cancer surveillance, treatment, and family counseling.
- Patients qualify for germline genetic testing regardless of personal or family history
  - High risk localized PCa
  - N+ and M+ PCa
- Precision therapies are now approved in prostate cancer – olaparib, rucaparib, pembrolizumab