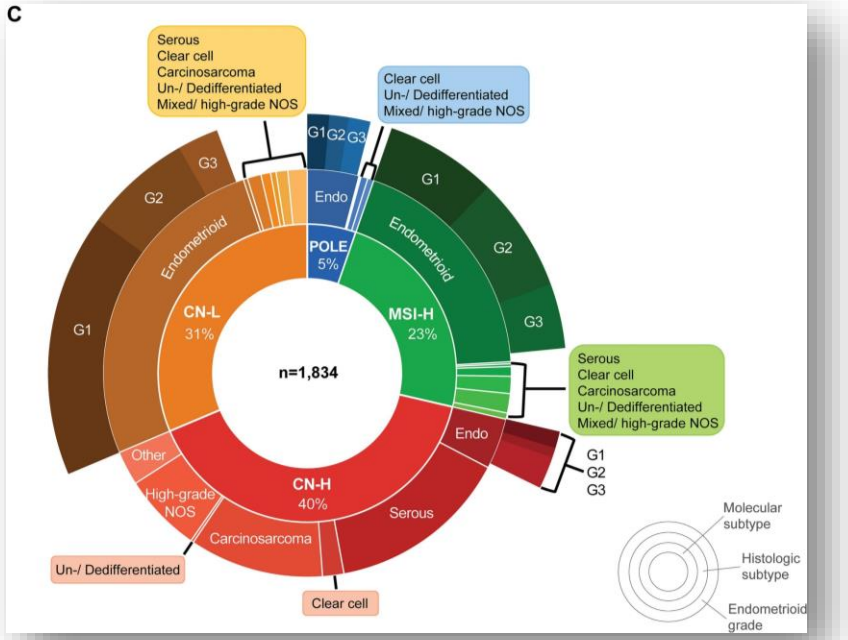
Memorial Sloan Kettering
Cancer Center

Integration of Molecular Classification in The Primary Treatment of Endometrial Cancer

June 15, 2023

Nadeem R. Abu-Rustum, M.D.
Chief Gynecology Service
AVON Chair Gynecologic Oncology
Memorial Sloan Kettering Cancer Center
New York



Conflict of Interest Disclosure

Nadeem R. Abu-Rustum, M.D.

- GRAIL, study sponsor, paid to MSK
- NCCN Committee Chair

FIGURE 1 Ten leading cancer types for the estimated new cancer cases and deaths by sex, United States, 2023. Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

Estimated New Cases

Males				Females		
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**

Siegel RL, et al. CA Cancer J Clin. 2023

FIGURE 1 Ten leading cancer types for the estimated new cancer cases and deaths by sex, United States, 2023. Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

Estimated Deaths

Males				Females		
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

Siegel RL, et al. CA Cancer J Clin. 2023

Optimizing The Management of Endometrial Cancer

1. Diagnostic advances (Pathology & Lab)
2. Surgical standardization
3. Advancing adjuvant therapy

Memorial Sloan Kettering Cancer Center

Genomic Categorization of Endometrial Carcinoma: Implications for Diagnosis and Management

Surgeons working with Pathologists

Endometrial Cancer Classification Inspired by Bokhman JV. 1983

ENDOMETRIAL CARCINOMA PATHOGENETIC TYPES

TABLE 1

THE SIGNS OF TWO MAIN PATHOGENETIC TYPES OF ENDOMETRIAL CARCINOMA[a]

TYPE 1 **TYPE 2**

Done by Histotyping

J.V. Bokhman. (Leningrad USSR),Two pathogenetic types of endometrial carcinoma. Gynecol Oncol (1983)

30 Years Later
Molecular Profiling vs. Histotyping
Endometrial Carcinoma TCGA Subgroups:

- P53 abn, MMR-D, CN-L (NSMP), POLE
- Unable to classify into these 4 categories by histology alone
- CN-H P53-abn is prognostically unfavorable
- POLE is prognostically favorable

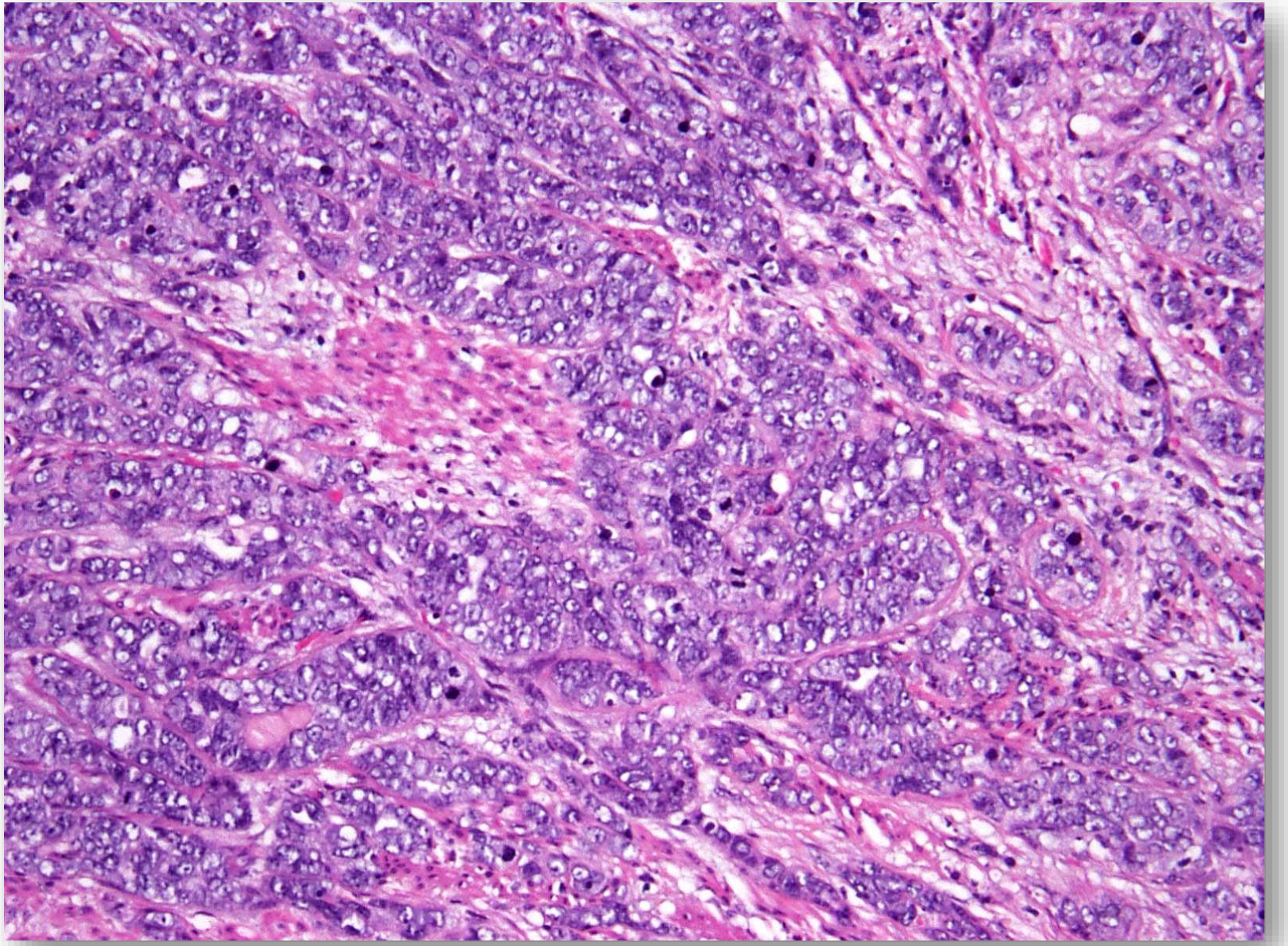
Integrated Genomic Characterization of Endometrial Carcinoma.
The Cancer Genome Atlas Network.
Nature 2013

List of Commonly Diagnosed High-Grade Endometrial Carcinoma

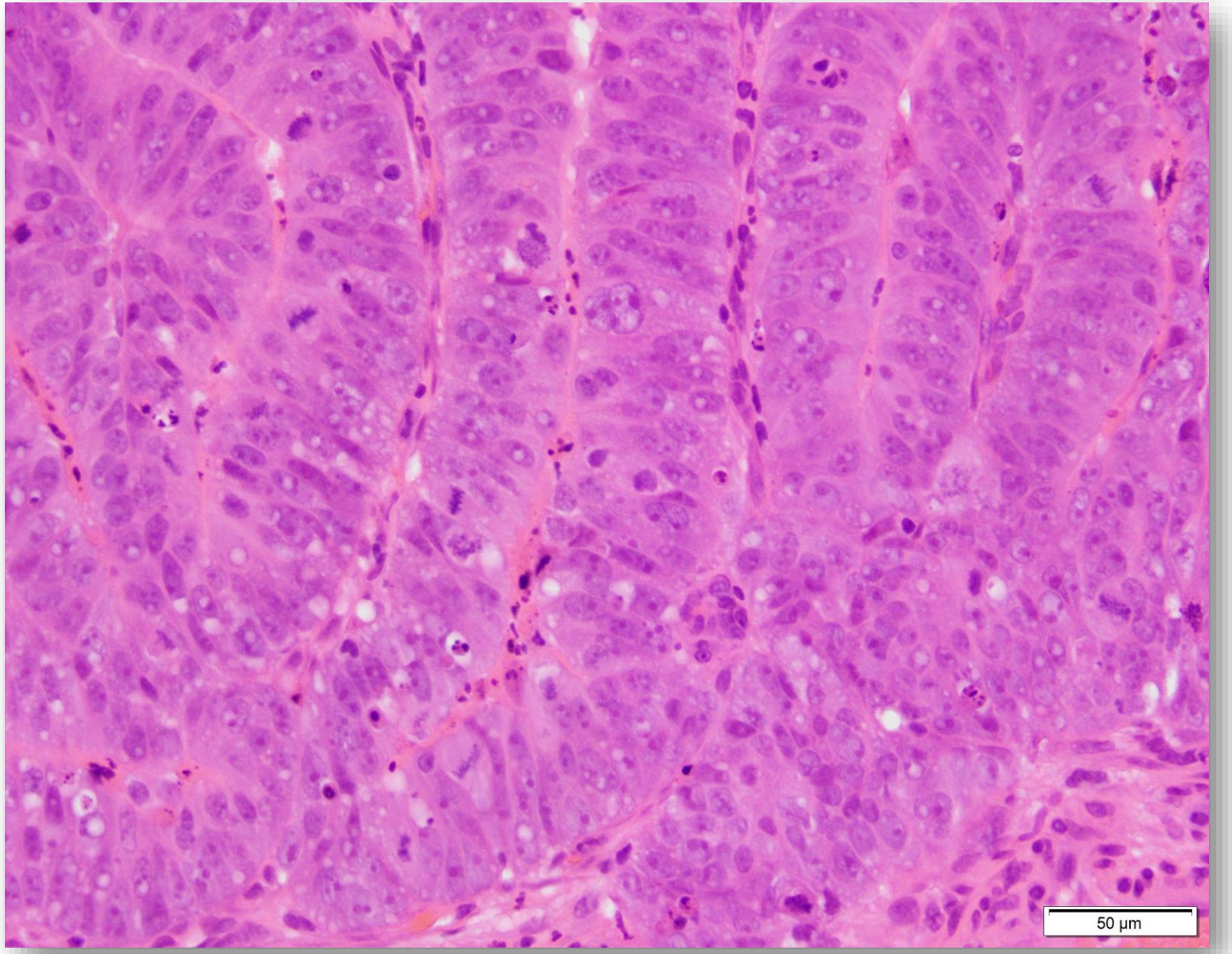
- FIGO grade 3 endometrioid
- Serous
- Clear cell
- Undifferentiated
- Carcinosarcoma/MMMT
- High-grade, NOS

Problem with High-Grade Endometrial Cancer

- Many (30-50%) high-grade EMCs are not prototypic.
- Very hard to classify using H&E alone.
- Examples:
  - "G3 endometrioid vs. serous carcinoma"
  - "G3 endometrioid vs. clear cell carcinoma"
  - "Serous vs. clear cell carcinoma"



Endometrioid vs. Serous



Endometrioid vs. Serous

Memorial Sloan Kettering Cancer Center

2013 - High Grade Endometrial Cancer: Poor Diagnostic Reproducibility

Vancouver General Hospital Series:

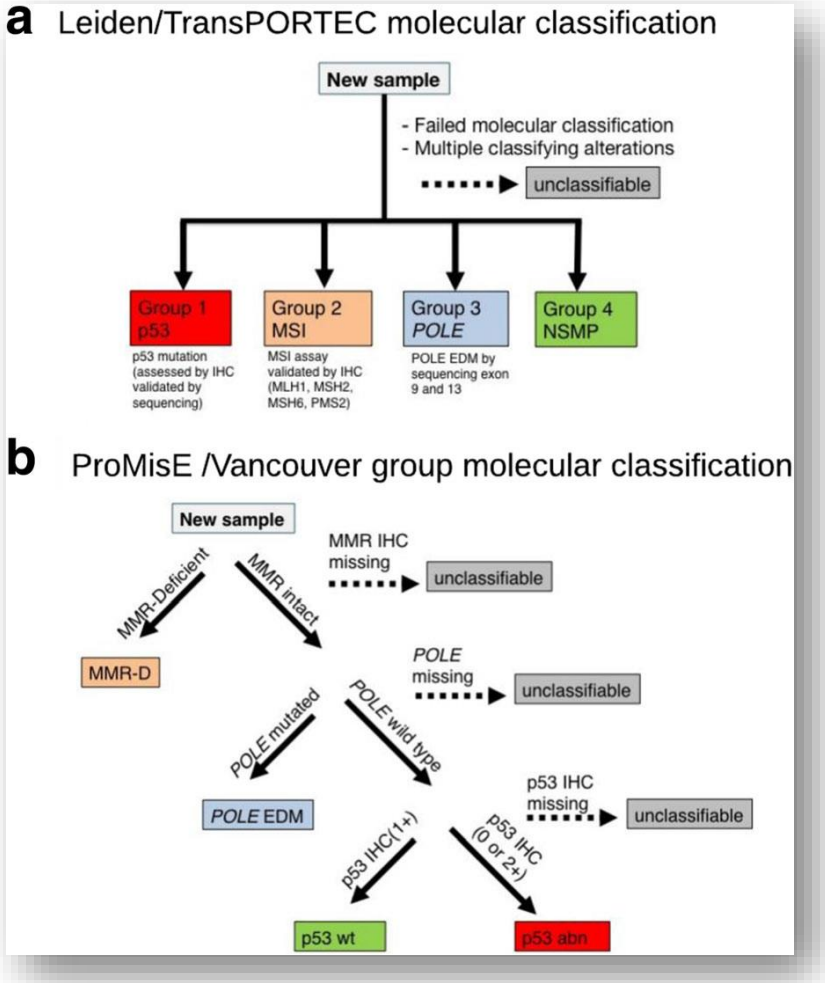
- **3** expert pathologists reviewed 56 cases.
- In only 35 (62%) cases, there was agreement between all 3 reviewers.
- In 20 **(36%) there was major disagreement.**
- Problem: **FIGO G3 endometrioid**
- There is a need for molecular tools to aid in the accurate and reproducible diagnosis of high-grade endometrial carcinoma subtype.

Gilks CB, Oliva E, Soslow RA. *Am J Surg Pathol*, 2013.

Interobserver Agreement in Endometrial Carcinoma Histotype Diagnosis Varies Depending on The TCGA-based Molecular Subgroup.
Hoang, Lien; et al. Am J of Surgical Pathology. February 2017.

- Limitations in the precise histologic classification of endometrial carcinomas highlights the importance of an ancillary molecular-based classification scheme.
- Problems with reproducible assignment of histotype/grade are not confined to 1 or 2 of the 4 molecular subgroups of endometrial carcinoma.
- **Morphology does not serve as a reliable surrogate for molecular classification, with the exception that pure serous carcinoma almost always resides in the p53 abn group.**

Schematic of Leiden/TransPORTEC & ProMisE Vancouver molecular classification systems



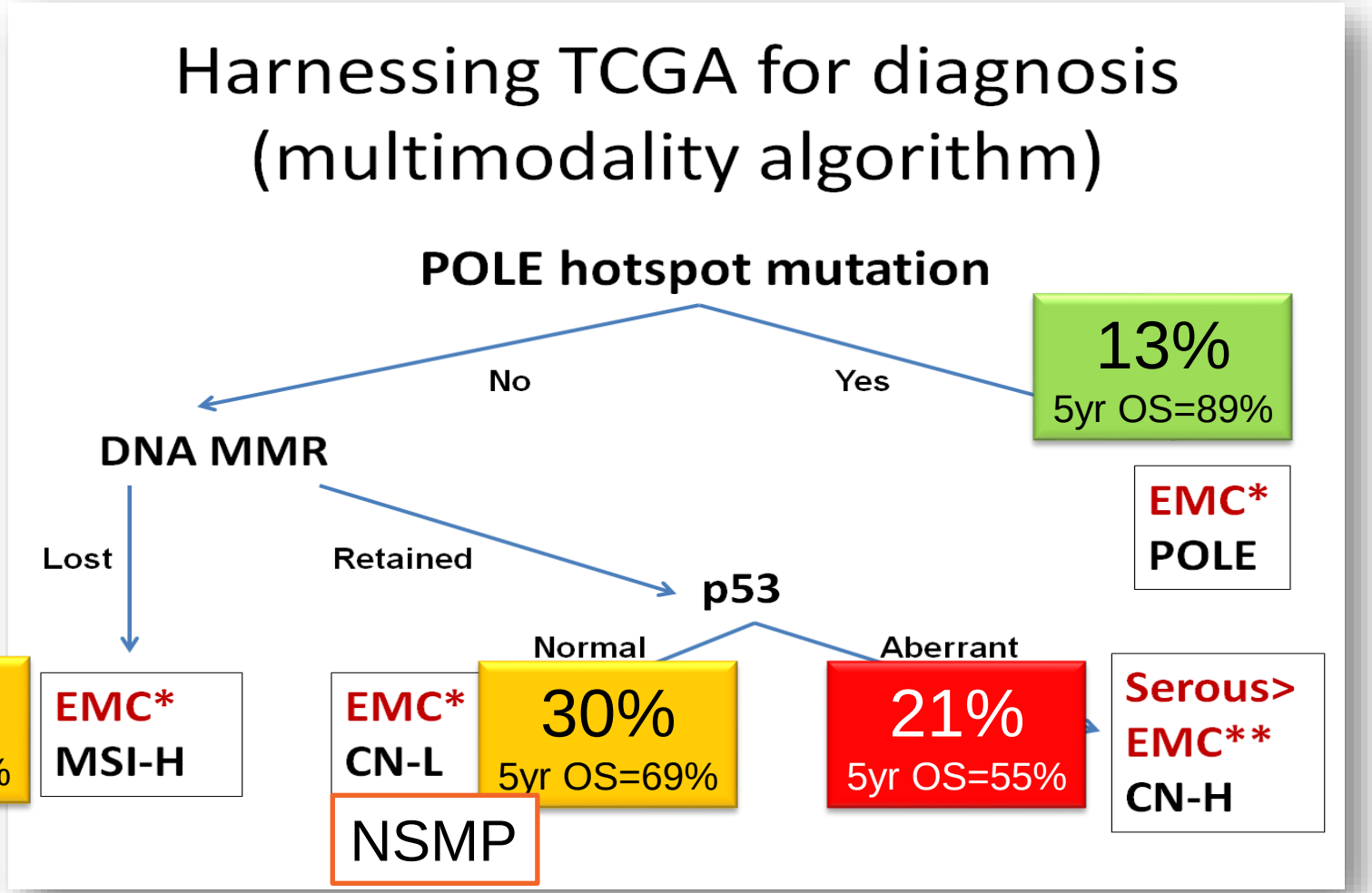
A Talhouk, B Gilks, J McAlpine Br J Cancer. 2015

ProMisE (Proactive Molecular Risk Classifier for Endometrial Ca)

Talhouk and McAlpine Gynecologic Oncology Research and Practice 2016

Memorial Sloan Kettering Cancer Center

Molecular Classification of 381 Patients G3 Endometrioid Endometrial Carcinoma



Tjalling Bosse, et al. Am J Surg Path 2018

Memorial Sloan Kettering Cancer Center

2016 NCCN Proposals

3-15-2016

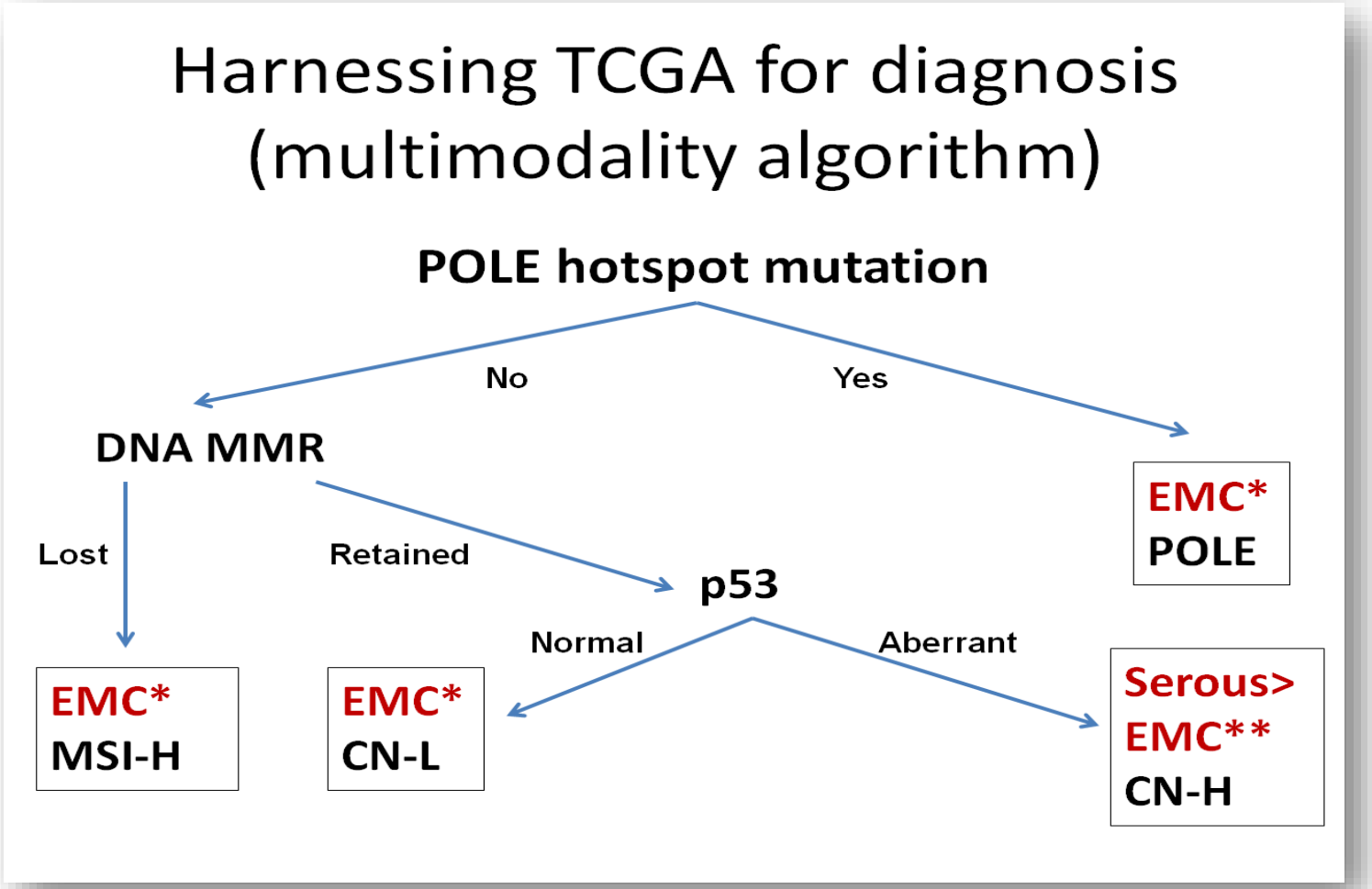
From MSKCC review:

For endometrial carcinomas, stage and tumor grade are the most robust prognostic indicators. They are also the data points that are most frequently used to determine type of surgery and whether to use adjuvant therapy. For this to have meaning, surgical stage must be determined and grade assignment must be reproducible. Neither is accomplished routinely, unfortunately. Although histologic subtype (histotype) is often said to be prognostically and therapeutically important, several publications have either reported or suggested that histotype loses significance when entered into a multivariate model that includes grade, stage, and most recently, TCGA cluster designation. TCGA cluster designation has recently been shown in small studies to be independently associated with clinical outcomes. The TCGA described 4 genomically defined clusters of endometrial carcinomas, comprising endometrioid and serous carcinomas, the two most common types of endometrial carcinoma and the types that are most often confused on histological examination.

Ultramutated endometrial carcinomas with POLE hotspot mutations had 100% relapse-free survivals despite frequently being high grade and displaying striking histological overlap with both serous carcinoma and MSI-H endometrioid carcinoma. Several other groups have by now confirmed the extraordinarily favorable clinical outcomes of these tumors. Serous and “serous-like” endometrioid carcinomas with Tp53 mutations and frequent amplifications and deletions (“copy number-high”) had the worst prognosis, while the MSI-H and “copy number-low” or “type I” endometrioid carcinomas clustered together with clinical outcomes that were intermediate between the POLE and copy number-high groups. Recently, the Vancouver and MSKCC groups replicated TCGA group assignments using POLE mutational analysis as well as immunohistochemistry for PMS2, MSH6 and p53. This resulted in Kaplan-Maier survival curves that were similar to that published by the TCGA. Other groups are known to be working on this. We therefore propose that all endometrial cancers undergo POLE mutational analysis and immunohistochemistry for PMS2, MSH6 and p53. The most obvious application is for risk refinement of intermediate-high risk patients. This paradigm allows for discrimination of low-risk endometrioid carcinomas that have a high-grade appearance as well as high-risk endometrial carcinomas whose histological appearance is ambiguous. Routine use of PMS2 and MSH6, both DNA mismatch repair markers, also accomplishes the SGO’s mandate to test or at least consider testing all endometrial cancers for Lynch syndrome risk assessment. There are other potential future applications, not the least of which is clinical trial eligibility and the development of patient- and tumor-tailored therapies.

Nadeem Abu-Rustum

Genomic Categorization of Endometrial Carcinoma



Proposed to NCCN March 2016.

NCCN Uterine Cancer Panel Presentation Philadelphia 4-24-2017

- Introduce in the NCCN guidelines the concept of a new genomic-based classification of endometrial cancers and the potential applications in research and clinical care.
- To highlight the emerging importance of a molecular-based classification over a purely morphologic classification scheme.

•Talhouk and McAlpine Gynecologic Oncology Research and Practice 2016

•Hoang, Lien; Talhouk, Aline; McConechy, Melissa; Huntsman, David; McAlpine, Jessica; Soslow, Robert; Gilks, Blake. Am J of Surgical Pathology. February 2017.

NCCN Uterine Cancer Panel Presentation Philadelphia 5-21-2018

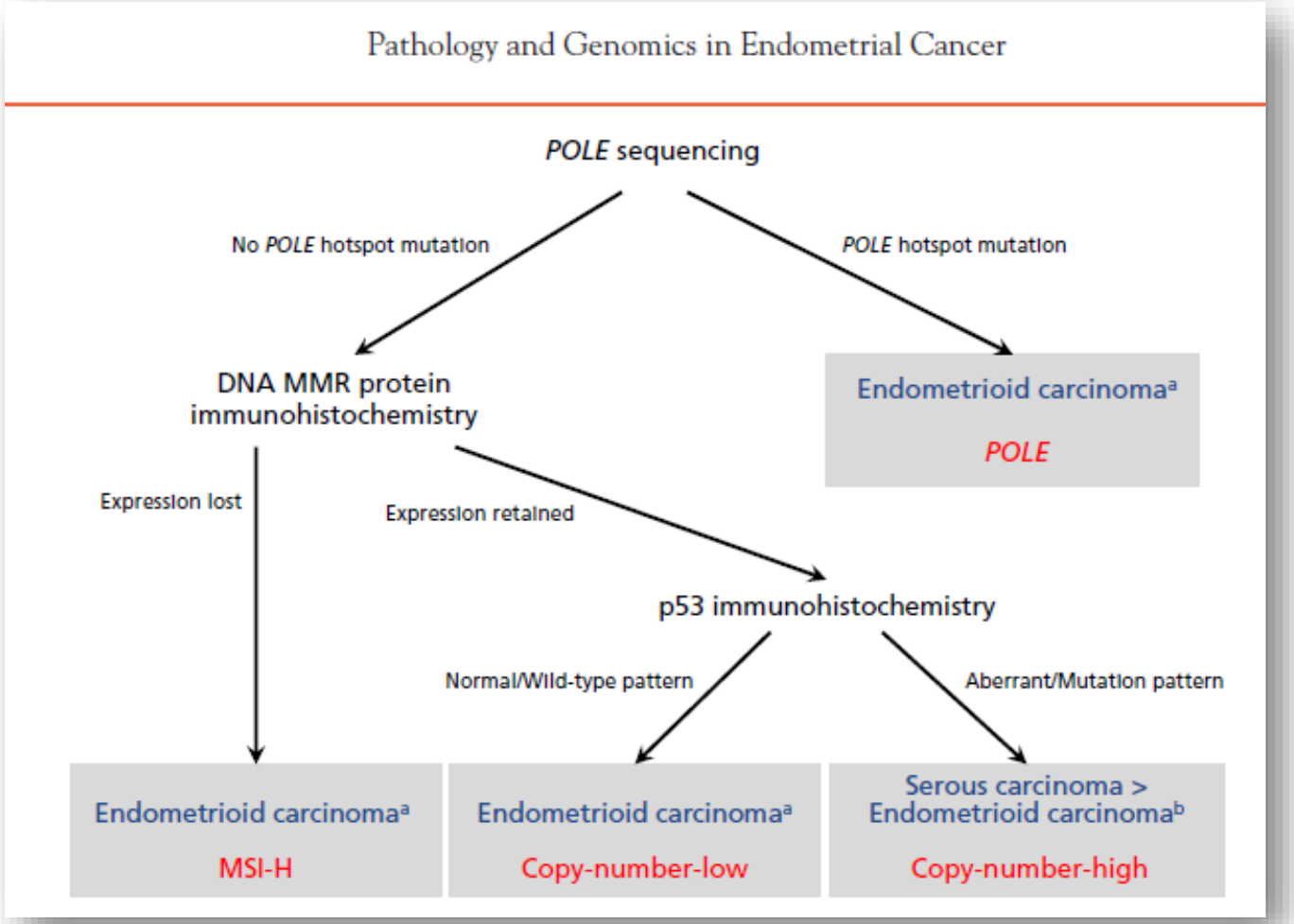
- The concept of genomic-based classification of endometrial cancers.
- Highlight the emerging importance of a molecular-based classification over a purely morphologic classification scheme.

Talhouk and McAlpine Gynecologic Oncology Research and Practice 2016

Hoang, Lien, et al. Am J of Surgical Pathology. February 2017.

Murali R, et al. JNCCN 2018

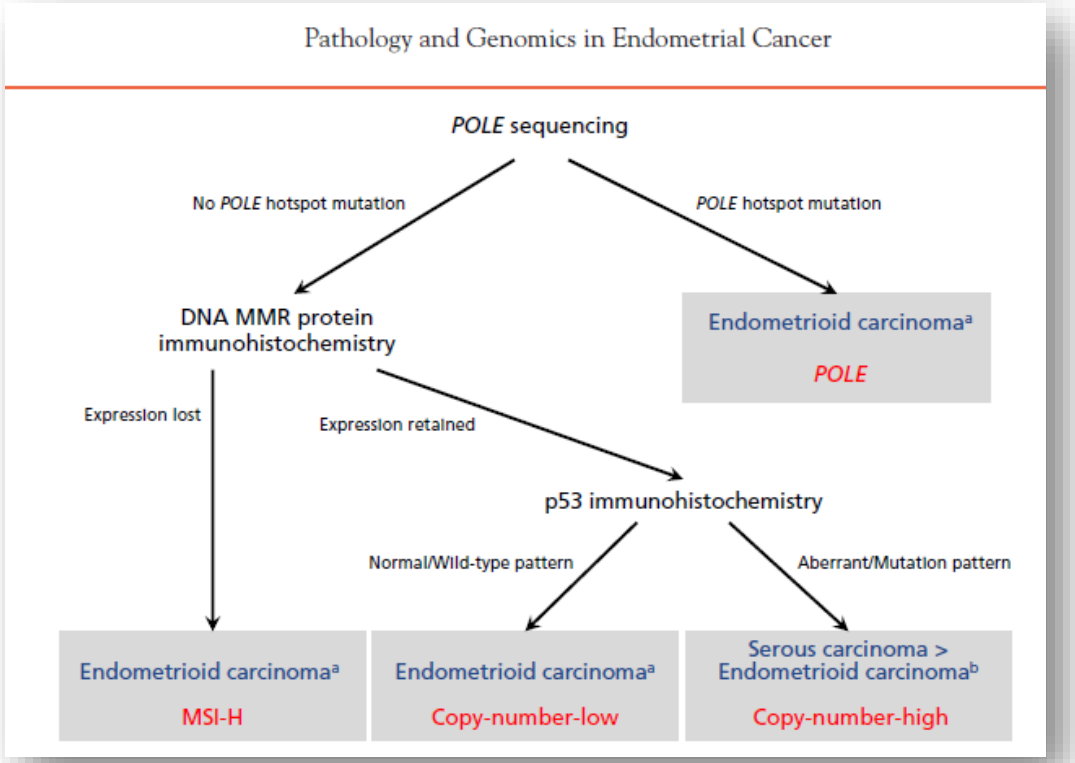
Evolving Roles of Histologic Evaluation and Molecular/Genomic Profiling in the Management of Endometrial Cancer



Murali R, et al. JNCCN 2018

Memorial Sloan Kettering Cancer Center

Evolving Roles of Histologic Evaluation & Molecular/Genomic Profiling in the Management of Endometrial Cancer



Murali R, et al. JNCCN 2018

A subset of POLE tumors may be MMR-deficient, and *POLE* exonuclease domain mutation (EDM) are associated with a favorable outcome, the *POLE* status should be determined first or in parallel to MMR.

Given that *TP53* alterations can be found in a subset of *POLE* and MMRd tumors, and that the clinical behavior between *bona fide TP53* altered copy-number high tumors and those with POLE+p53 or MMRd+p53 is distinct, one should not start from the “p53 end of the scheme” as the MMRd+p53 and the POLE+p53 will be missed.

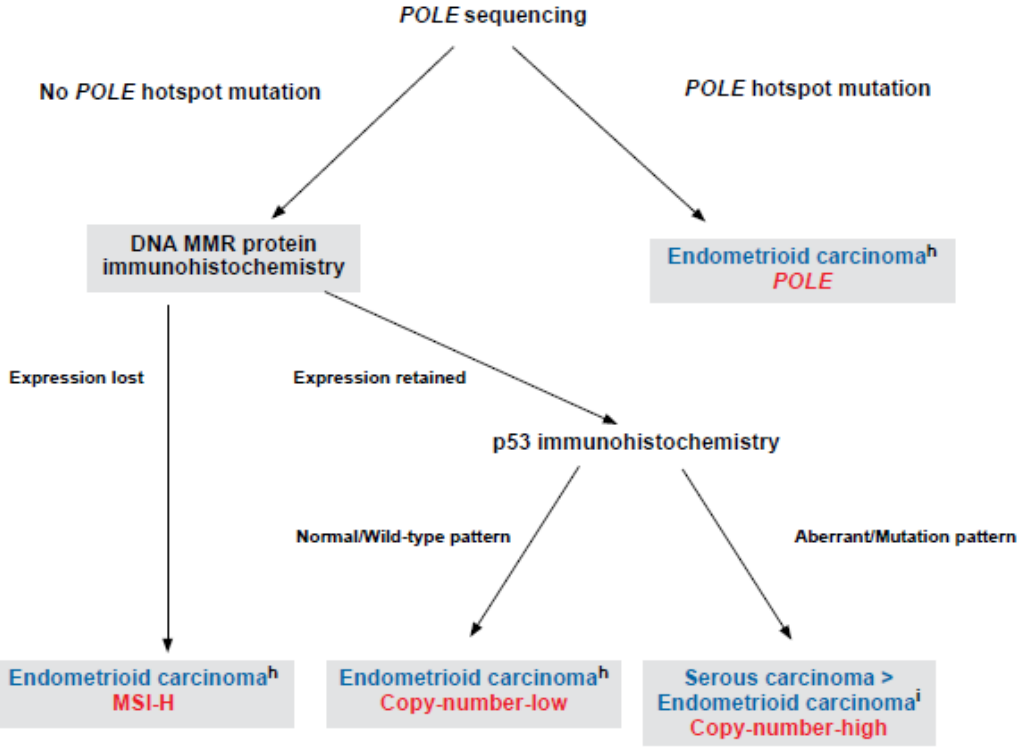
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Endometrial Carcinoma
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA[f,g]



[f]Reproduced with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g]Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas (blue represents histotype; red represents TCGA genomic class).
[h]May also apply to clear cell carcinomas.
[i]This algorithm does not distinguish between histotypes of *TP53*-mutated copy-number-high tumors (ie, high-grade endometrioid carcinoma, serous carcinoma, and clear cell carcinoma).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

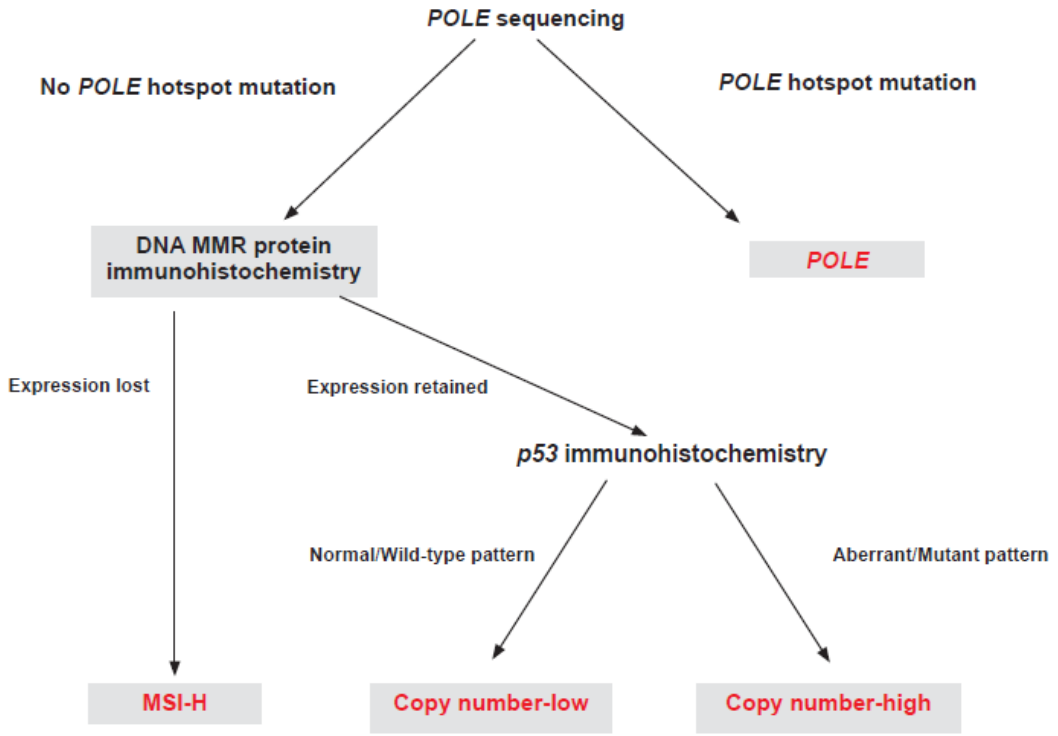
References
Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Endometrial Carcinoma
NCCN Evidence Blocks™

PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center)[f,g]

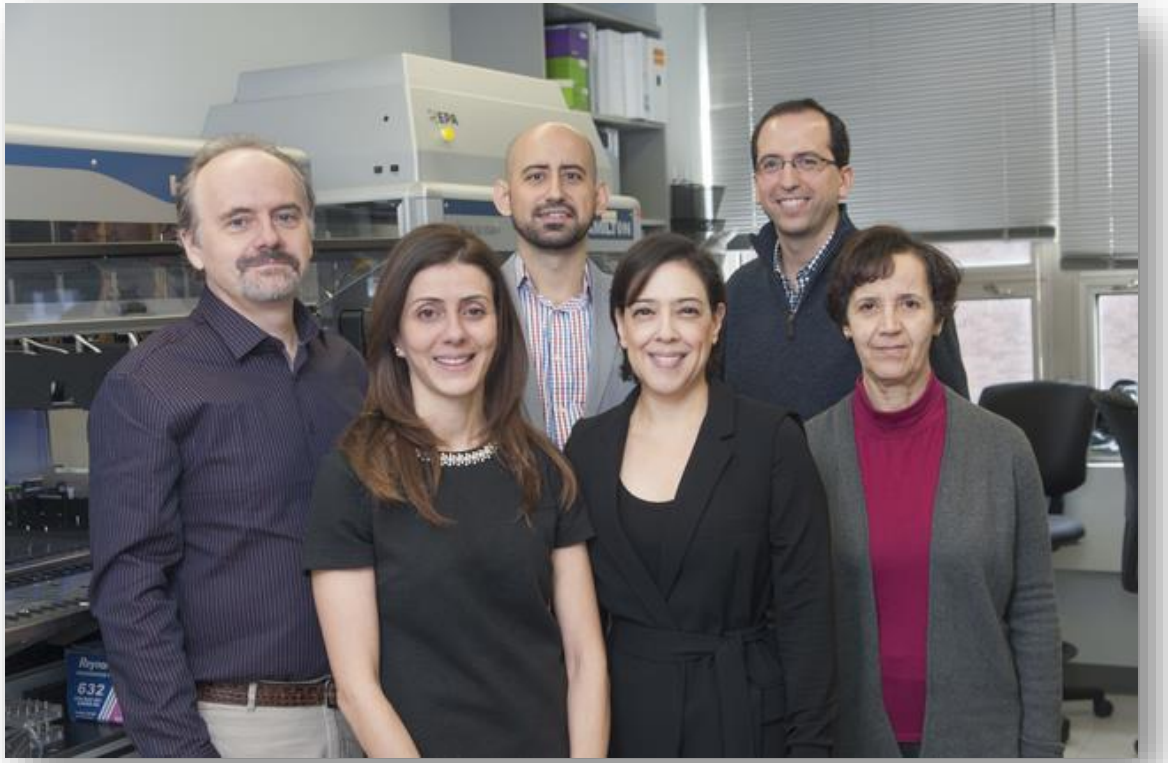


[f] Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g] Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

MSK-IMPACT™

"Integrated Mutation Profiling of Actionable Cancer Targets"
Targeted Next Generation Sequencing (NGS)

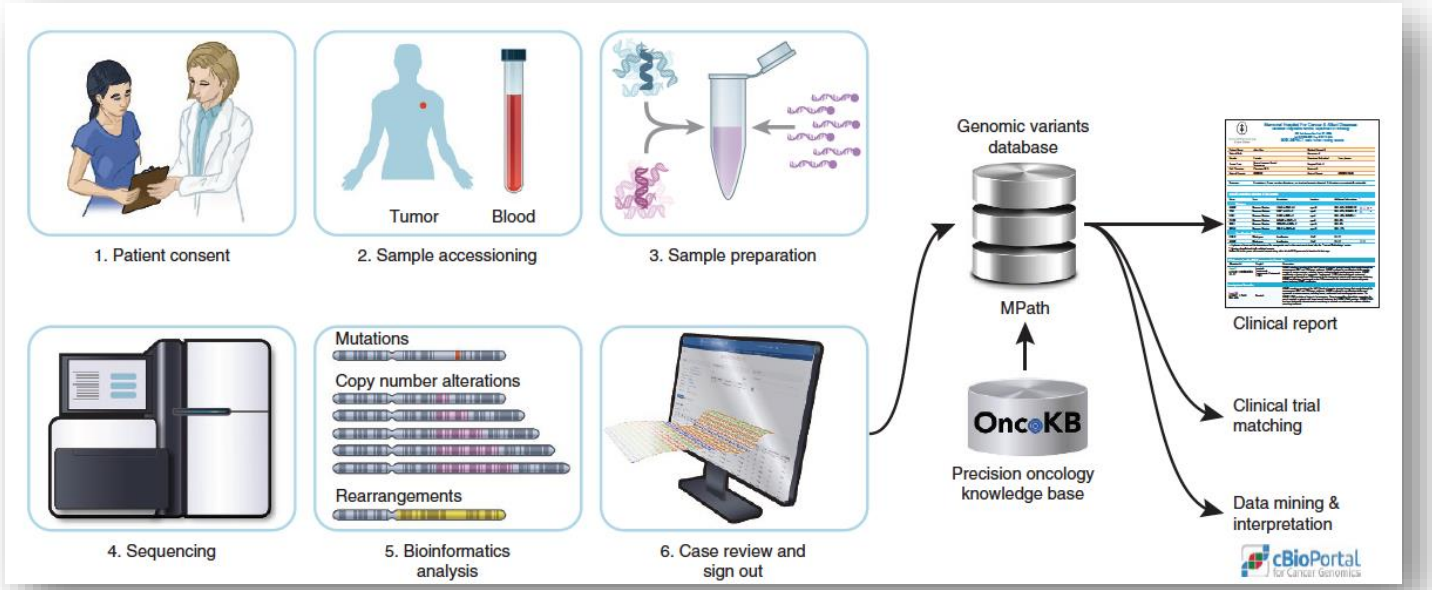


Ryma Benayed, Maria Arcila, and Khedoudja Nafa. Back row, from left to right: Marc Ladanyi, Ahmet Zehir, and Michael Berger.

Memorial Sloan Kettering Cancer Center

MSK-IMPACT™

"Integrated Mutation Profiling of Actionable Cancer Targets"
Targeted Next Generation Sequencing (NGS)



- Targets 505 cancer-related genes
  - Somatic alterations
    - Mutations
    - Copy number alteration
    - Fusion genes
  - 90 genes germline
- MSI status
- TMB status

- 86,953 samples MSK-IMPACT (May 3, 2022)
  - 2,986 endometrial cancer samples
- 11,947 FusionPlex ARCHER sequencing (fusion detection)
  - 250 uterine sarcoma

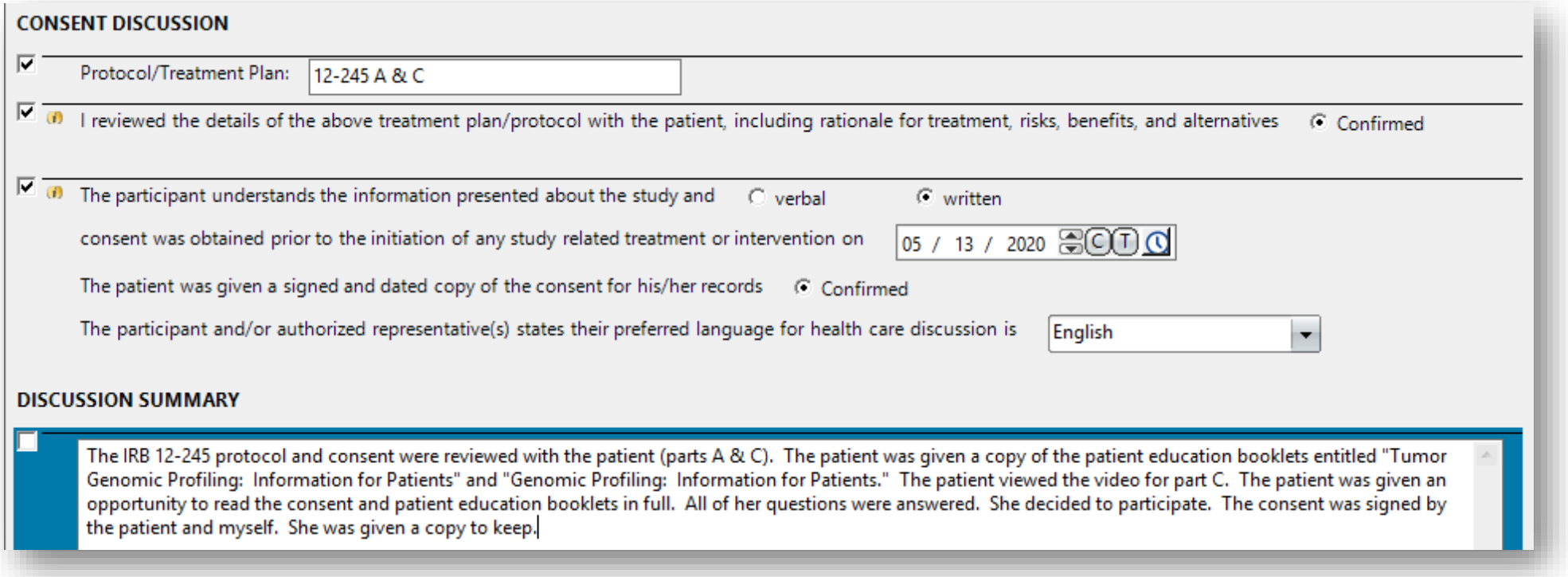
Zehir Ahmet, et al, Nat Med 2017; cBioPortal

Memorial Sloan Kettering Cancer Center

Nov. 15, 2017 FDA Authorized MSK-IMPACT Integrated Mutation Profiling of Actionable Cancer Targets

- The US Food and Drug Administration announced the authorization of MSK-IMPACT™ to look for genetic mutations and other alterations in patients' tumors (detects genetic mutations in 468 genes).
- MSK-IMPACT, has been used to analyze the tumors of people treated at MSK since January 2014.
- It is based on high-throughput next-generation sequencing.
- When the test was first developed, it looked for alterations in 341 cancer-associated genes. Today, it looks for alterations in 505 genes.

12-245 Parts A & C



CONSENT DISCUSSION

Protocol/Treatment Plan: 12-245 A & C

I reviewed the details of the above treatment plan/protocol with the patient, including rationale for treatment, risks, benefits, and alternatives — Confirmed

The participant understands the information presented about the study and — verbal — written

consent was obtained prior to the initiation of any study related treatment or intervention on 05 / 13 / 2020

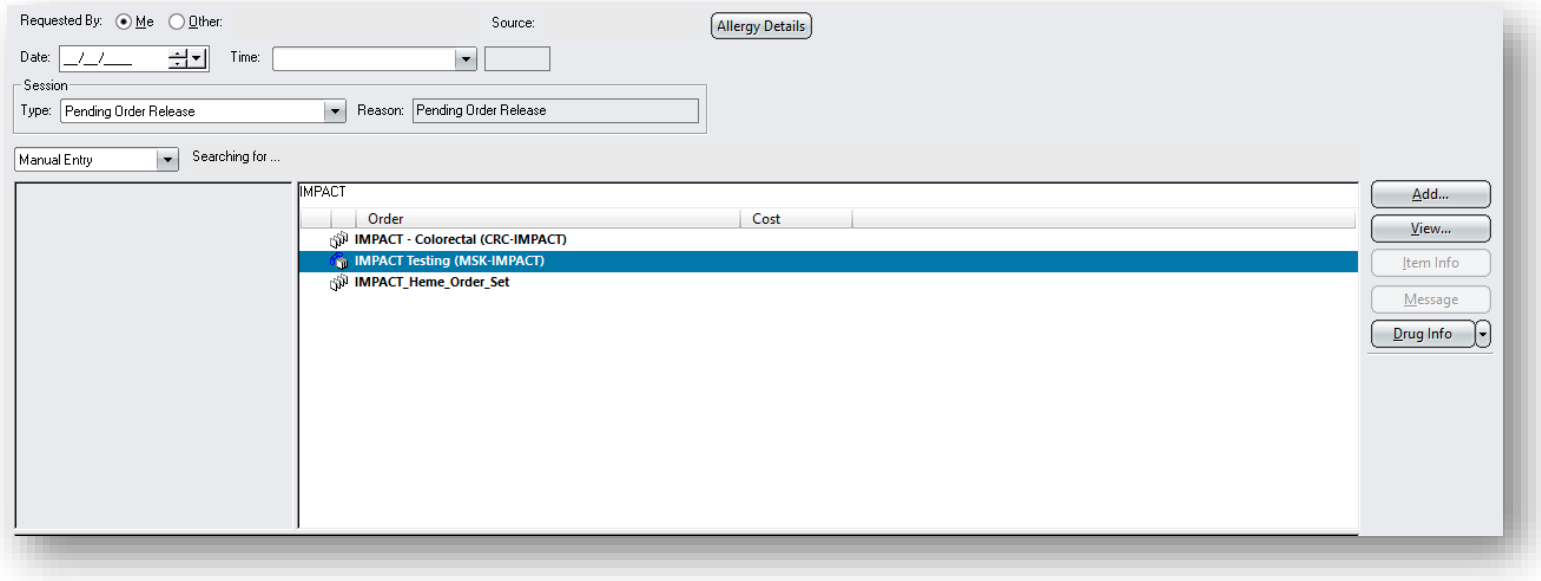
The patient was given a signed and dated copy of the consent for his/her records — Confirmed

The participant and/or authorized representative(s) states their preferred language for health care discussion is English

DISCUSSION SUMMARY

The IRB 12-245 protocol and consent were reviewed with the patient (parts A & C). The patient was given a copy of the patient education booklets entitled "Tumor Genomic Profiling: Information for Patients" and "Genomic Profiling: Information for Patients." The patient viewed the video for part C. The patient was given an opportunity to read the consent and patient education booklets in full. All of her questions were answered. She decided to participate. The consent was signed by the patient and myself. She was given a copy to keep.

IMPACT – Clinical Testing



On March 25, 2016, we started offering MSK IMPACT to all new endometrial cancer cases presenting in surgery clinics (we had a budget to test 200 cases)

This is now a clinical test

- Requires consent, “Informed Consent for the MSK-IMPACT Test”
- Billable

Memorial Sloan Kettering Cancer Center

Molecular classification of endometrial cancer: surrogate

Analyses to be performed

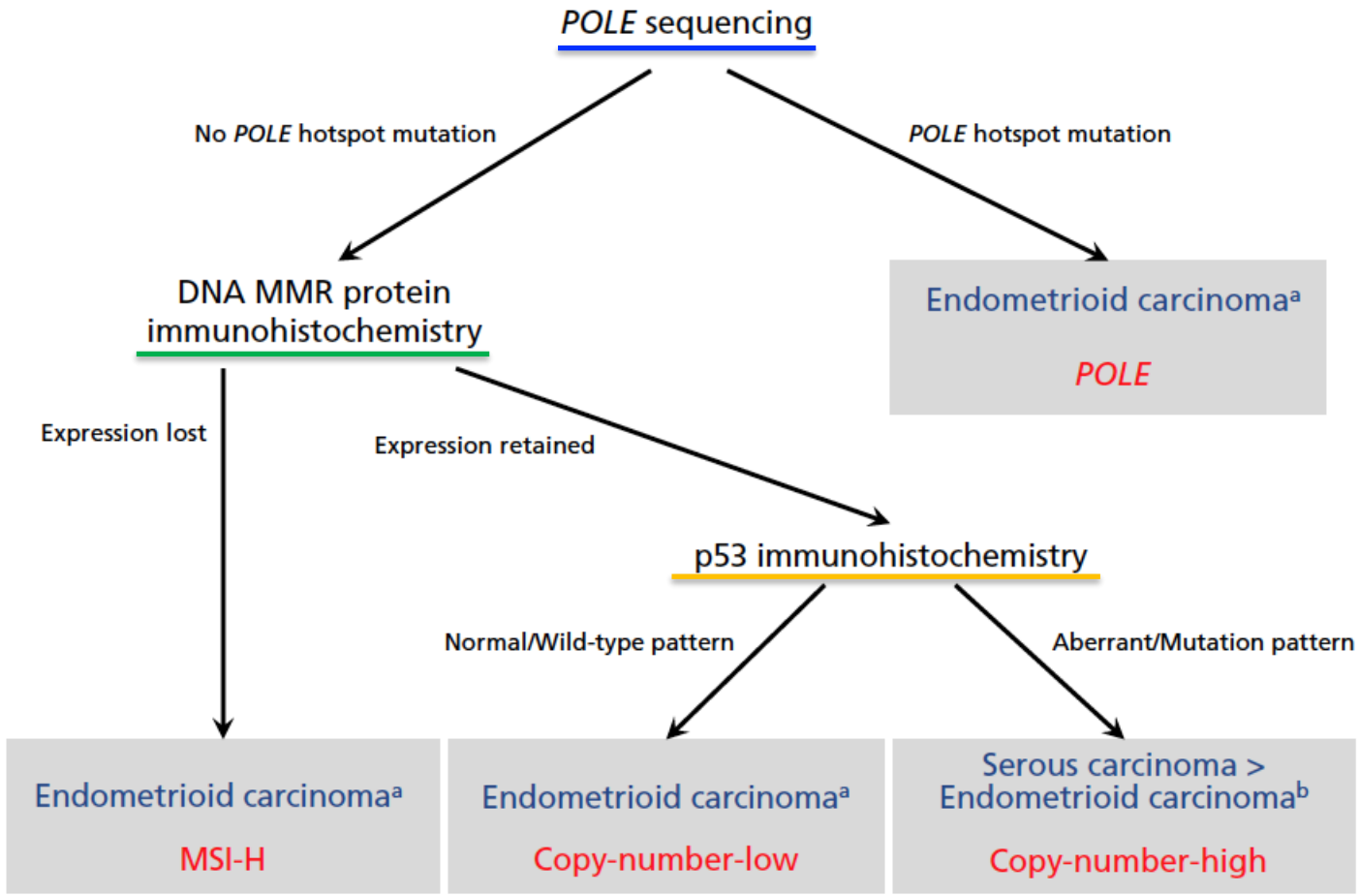
1. *POLE* exonuclease domain mutation analysis
2. IHC DNA mismatch repair proteins
3. IHC p53

POLE

Protein change	Nucleotide substitution
P286R	c.857C>G
V411L	c.1231G>T/C
S297F	c.890C>T
S459F	c.1376C>T
A456P	c.1366G>C
F367S	c.1100T>C
L424I	c.1270C>A
M295R	c.884T>G
P436R	c.1307C>G
M444K	c.1331T>A
D368Y	c.1102G>T

MSK-IMPACT:

- *POLE* mutation
- *TP53* mutation
- MSI status
- Tumor mutation burden



Murali et al, JNCCN 2018; Leon-Castillo et al, J Path 2018

Somatic tumor profiling: MSK *IMPACT*

"Integrated Mutation Profiling of Actionable Cancer Targets"
Targeted Next Generation Sequencing (NGS)

Memorial Hospital For Cancer & Allied Diseases
Molecular Diagnostics Service, Department of Pathology
1275 York Avenue New York, NY, 10065
Tel: (212) 639-8280 | Fax: (212) 717-3515
MSK-IMPACT Testing Report

Gene	Protein Change	Annotation	Mutation Type	Allele Freq	Copy #
PIK3CA	*Q546K*	3B	Missense	0.59	Diploid
TP53	*R248Q*		Missense	0.59	Diploid
IKZF1	*R360H*		Missense	0.22	Diploid
LATS1	*P452A*		Missense	0.13	Diploid
ERBB2	AMP	3B			
CCNE1	AMP				

The power of MSK *IMPACT*

Cancer Gene Exons
All protein-coding exons of 505 genes

- Actionable mutations
- Targets of investigational agents
- Frequent mutations in cancer
- Cancer susceptibility genes

Cancer Gene Introns
70 introns of 20 rearranged genes

Non-coding Regions

- TERT promoter
- Microsatellites
- >1000 common SNPs

Memorial Sloan Kettering Cancer Center

MSK IMPACT Part-C Report

"Integrated Mutation Profiling of Actionable Cancer Targets"

DIAGNOSTIC INTERPRETATION:

TEST PERFORMED:
Secondary Germline MSK-IMPACT (Version 3):
ALK, APC, ATM, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN2A, CEBPA, CHEK2, CTR9, DICER1, EGFR, EPCAM, ERBB2, ERCC3, ETV6, FANCA, FANCC, FH, FLCN, GATA2, GREM1, HOXB13, HRAS, KIT, KRAS, LZTR1, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NRAS, NTHL1, PALB2, PAX5, PDGFRA, PHOX2B, PMS2, POLD1, POLE, PTCH1, PTEN, RAD51, RAD51B, RAD51C, RAD51D, RB1, RECQL, REST, RET, RTEL1, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERT, TGFBR1, TGFBR2, TMEM127, TP53, TRIP13, TSC1, TSC2, VHL, WT1, YAP1

RESULTS:
Negative. No Variant of Clinical Significance Identified.

Test results should always be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete. If results obtained do not match the clinical findings, additional testing should be considered.

Memorial Sloan Kettering Cancer Center

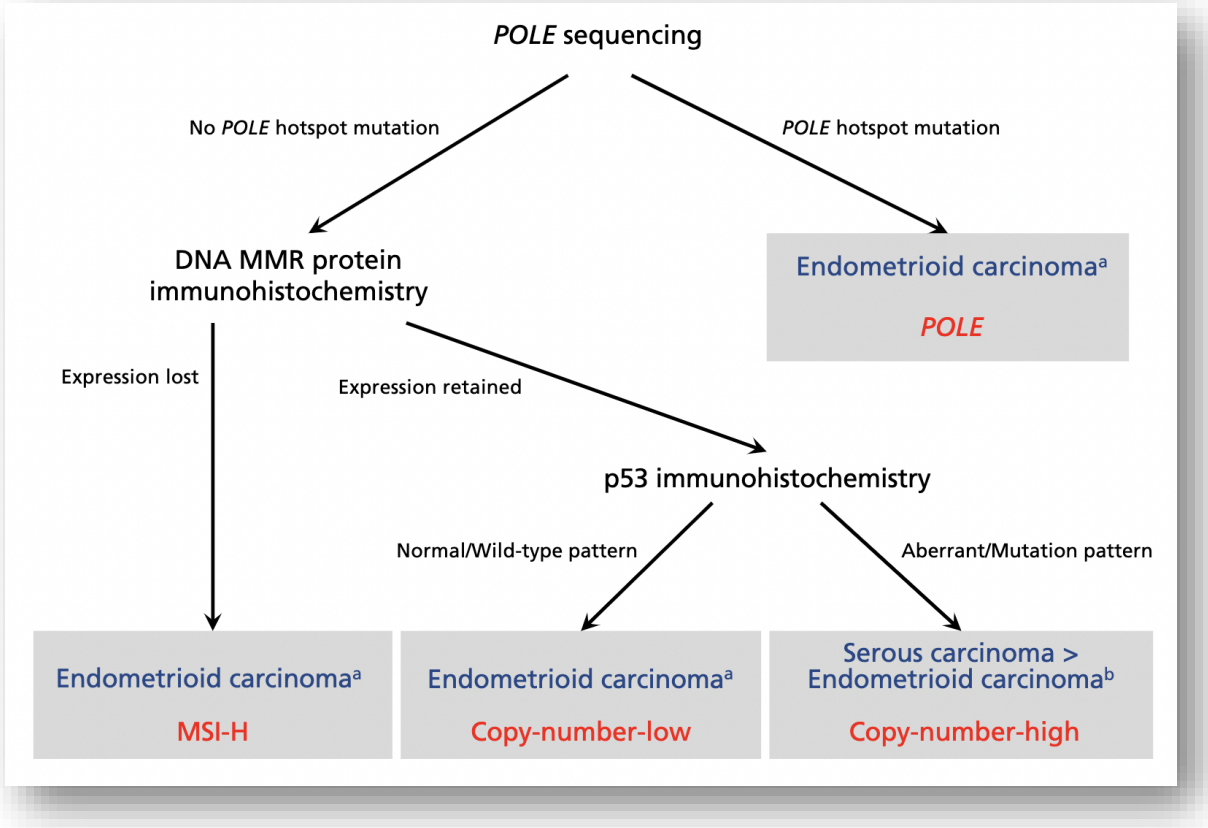
Molecular Classification of Endometrial Carcinomas: A Single Institution Review

Rios-Doria E, et al (MSKCC) Gynecol Oncol 2023

@TeamEndo_MSK

Molecular Surrogate Classification

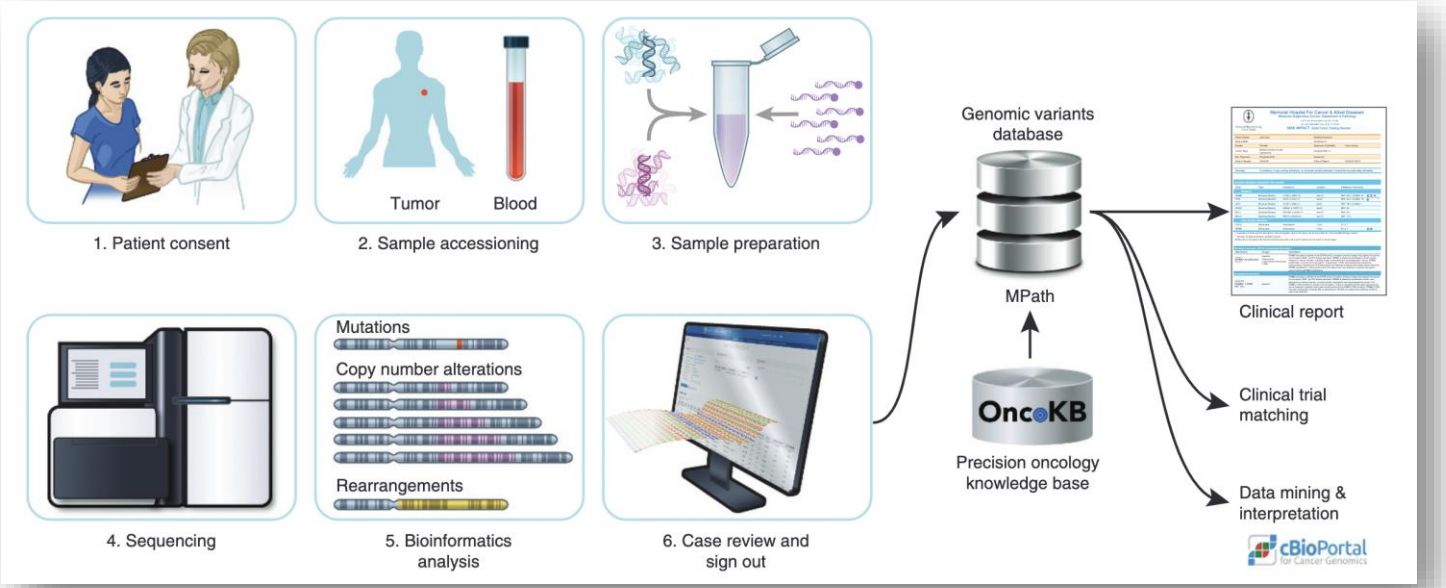
- Hybrid approach:
  - *POLE* exonuclease domain mutations
  - DNA MMR IHC
  - p53 IHC



Talhouk A, McConechy MK, Leung S, Yang W, Lum A, Senz J, et al. Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer. Cancer 2017;123:802–13.

Murali R, Delair DF, Bean SM, Abu-Rustum NR, Soslow RA. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Natl Compr Canc Netw 2018;16:201–9.

MSK-IMPACT



The genomic data extracted from the MSK-IMPACT assay, targets between 505 (2020) cancer-related genes, included somatic mutation count, POLE mutational status, TP53 mutation status, MSIsensor score, tumor purity, fraction of genome altered (FGA), and tumor mutational burden (TMB). POLE exonuclease domain hotspot mutations were defined based on Leon-Castillo et al. MSIsensor scores of ≥10 were considered MSI-H

Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med 2017;23:703–13.

Study Objectives

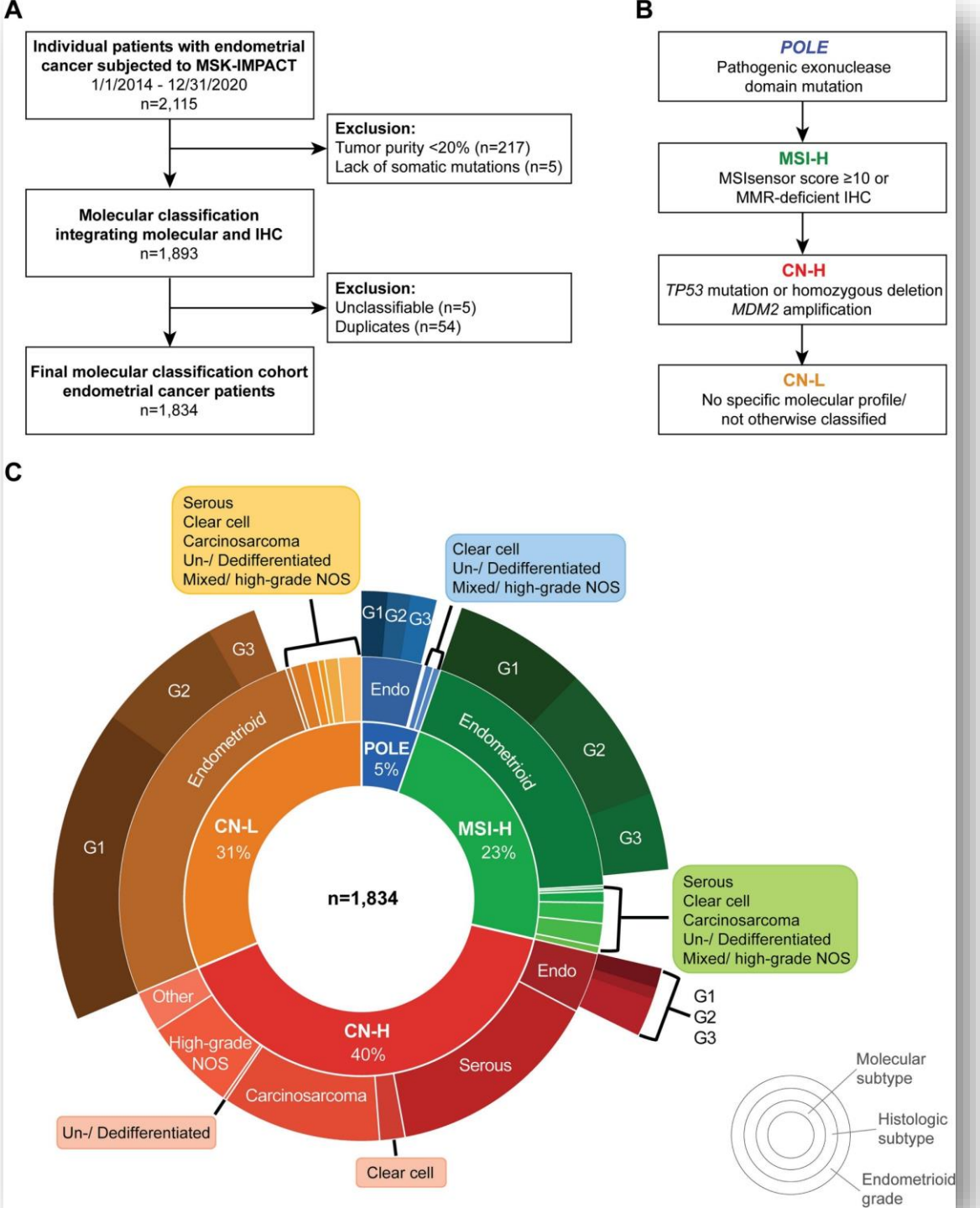
- Define a novel approach integrating next-generation sequencing and immunohistochemistry for the molecular classification of endometrial cancer

- Characterize the clinical and pathologic features of endometrial cancer molecular subtypes at Memorial Sloan Kettering Cancer Center

Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Methods

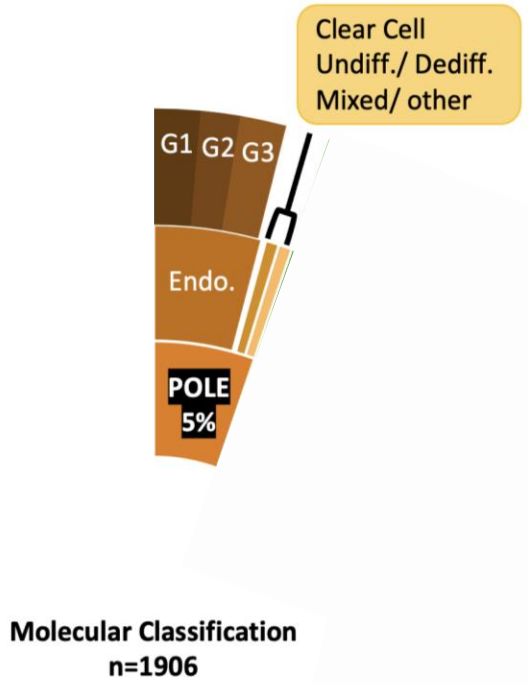
- All patients with endometrial cancer consented to genomic profiling and subjected to MSK-IMPACT from 2014 through 2020
- Clinical and pathology reports reviewed
- Exclusion criteria
  - Tumor purity < 20%, lack of somatic mutations, sarcoma histology
- Survival analysis for patients with upfront surgical staging and MSK-IMPACT performed



Memorial Sloan Kettering Cancer Center

Results

MSKCC TCGA Subtypes

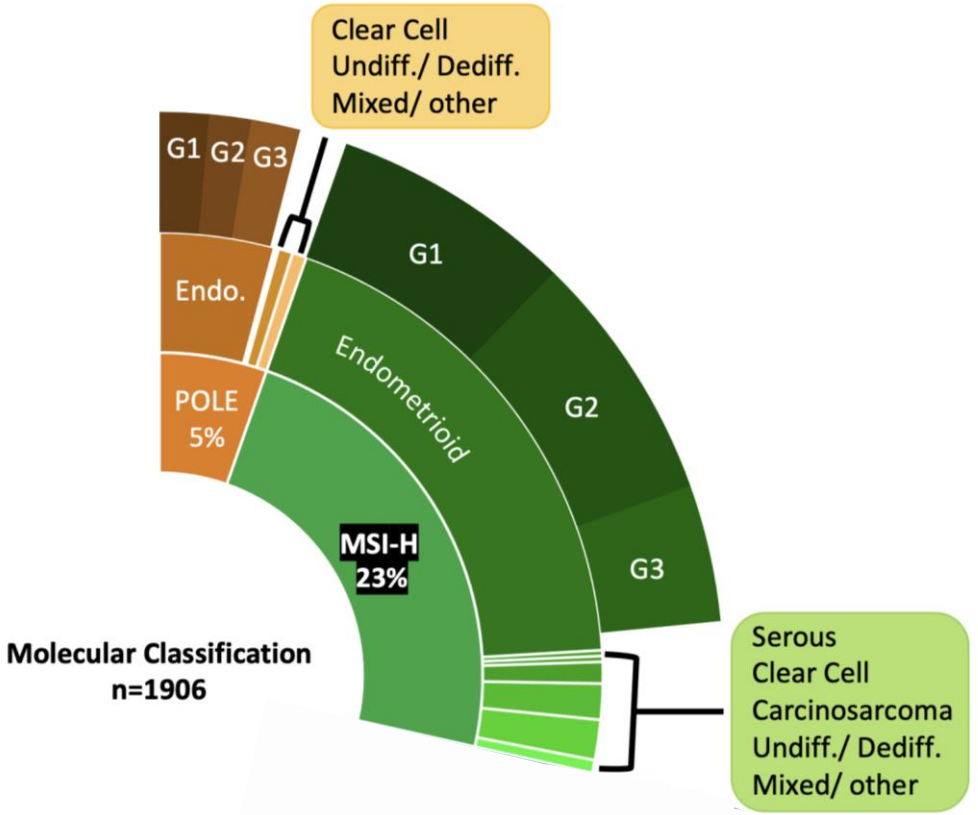


Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center

Results

MSKCC TCGA Subty

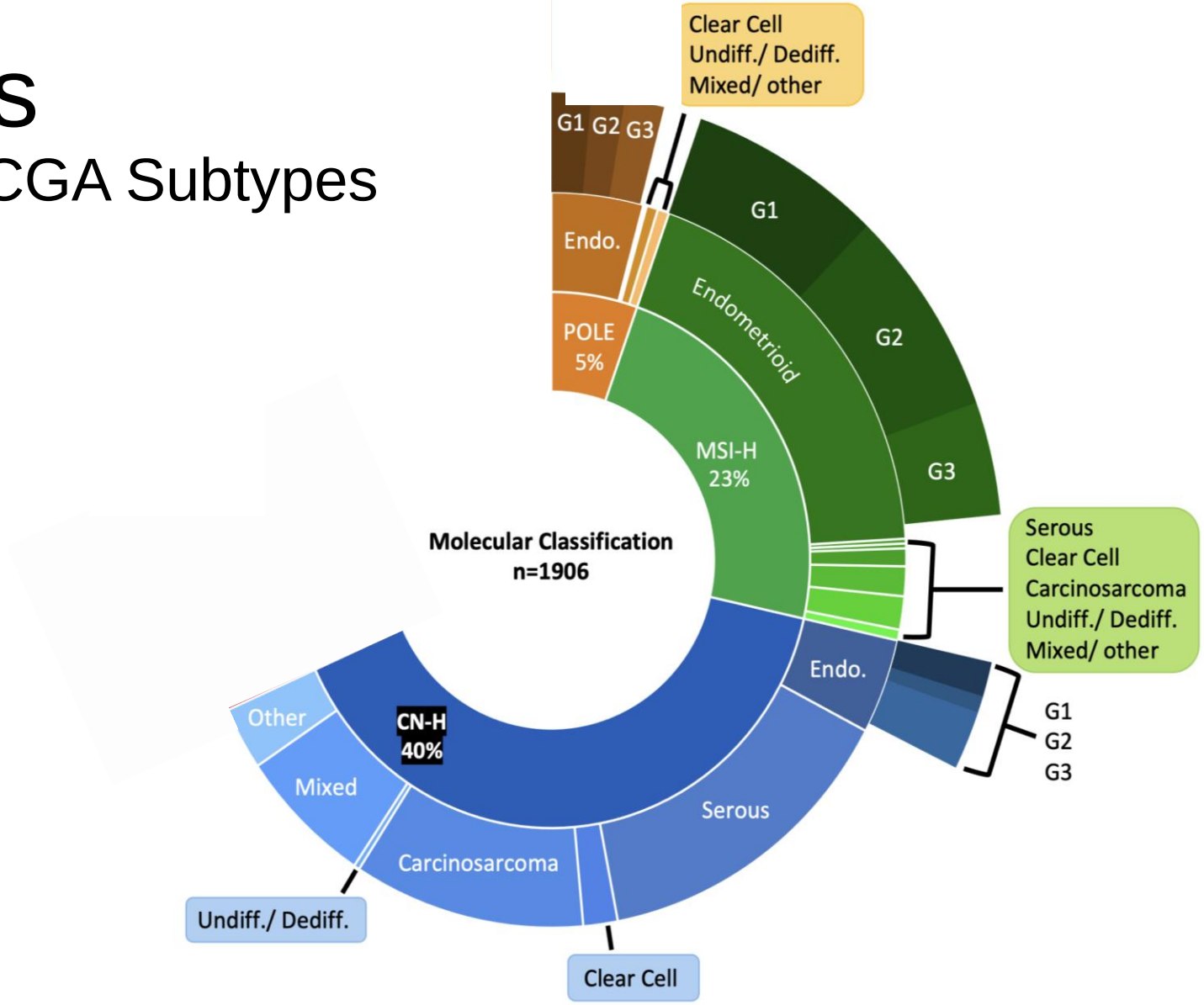


Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center

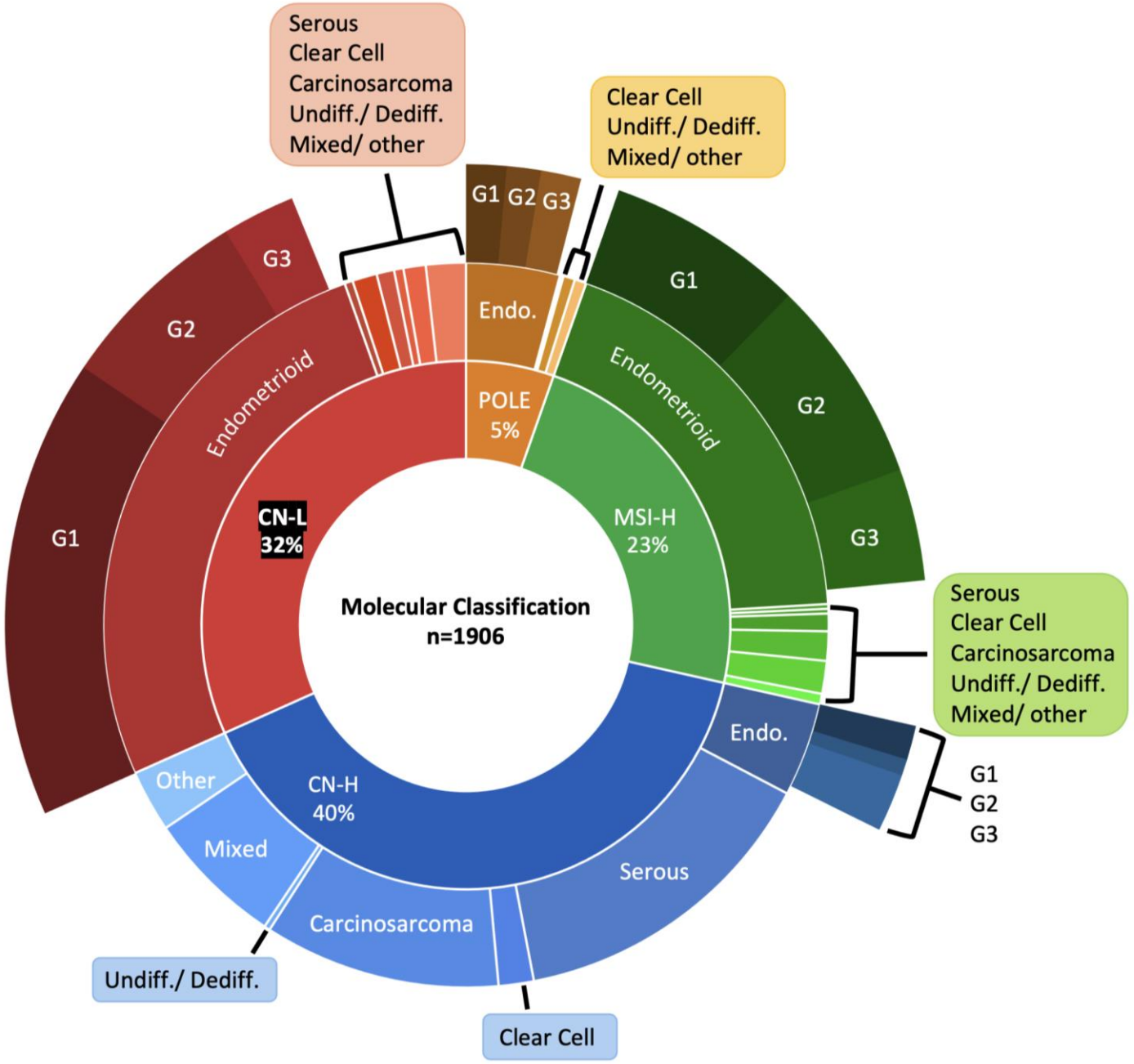
Results

MSKCC TCGA Subtypes



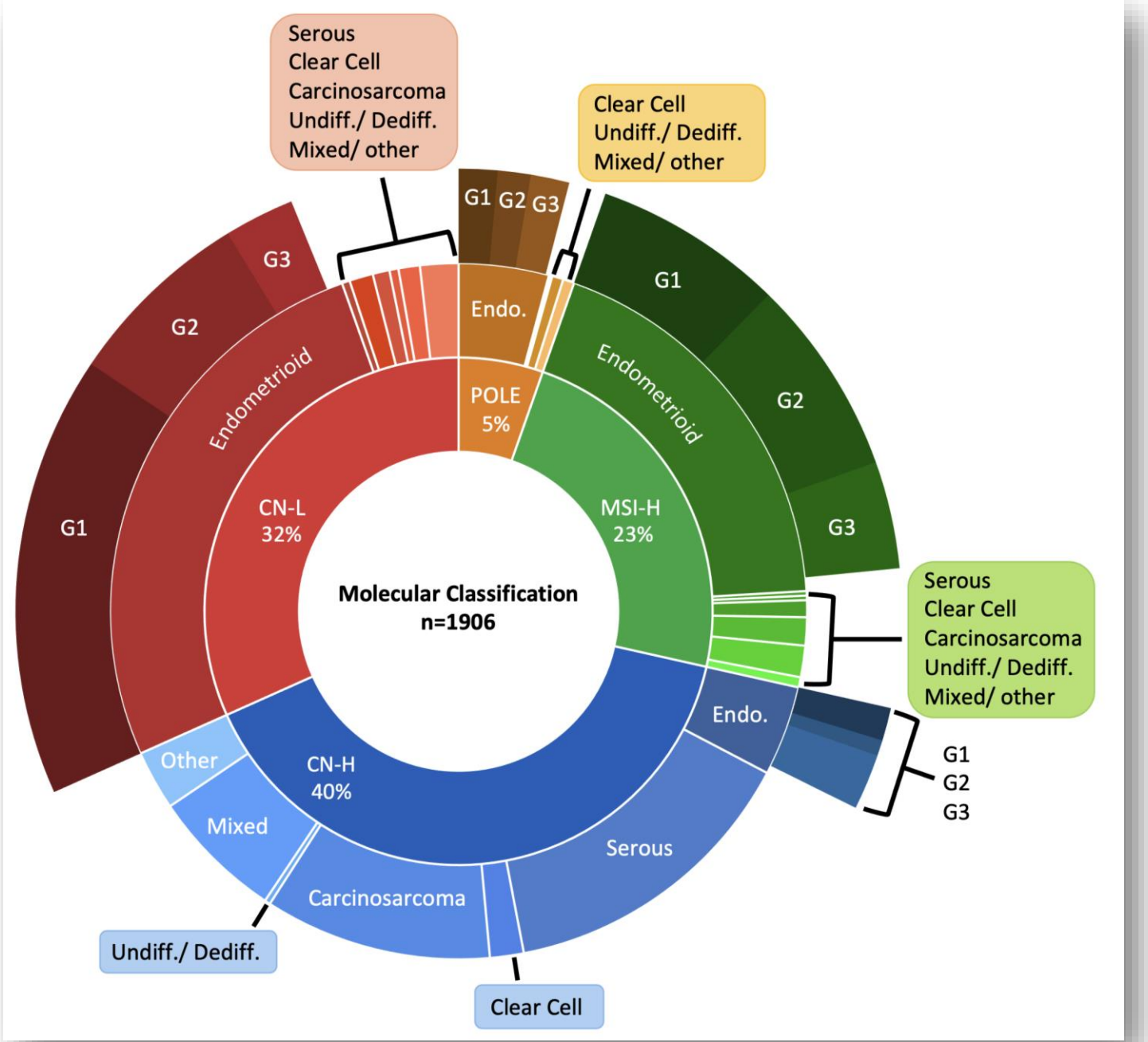
Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center



Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center

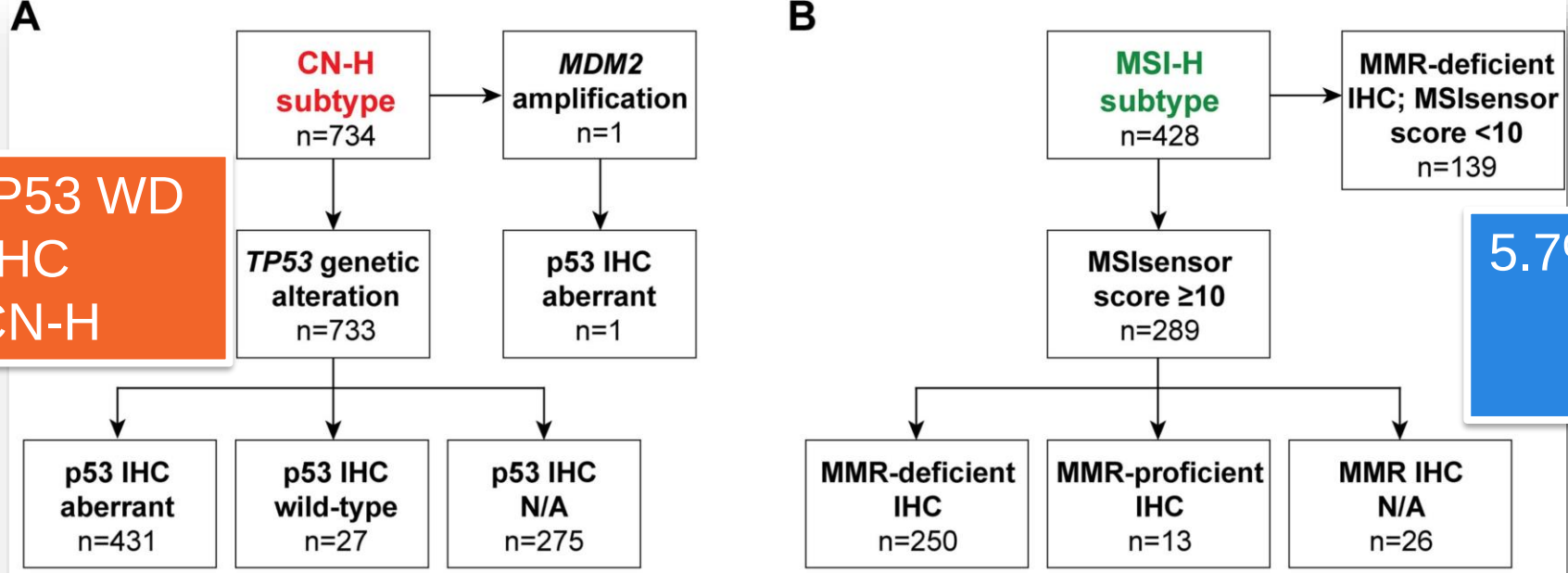


CN-H associated with non-endometrioid & G3

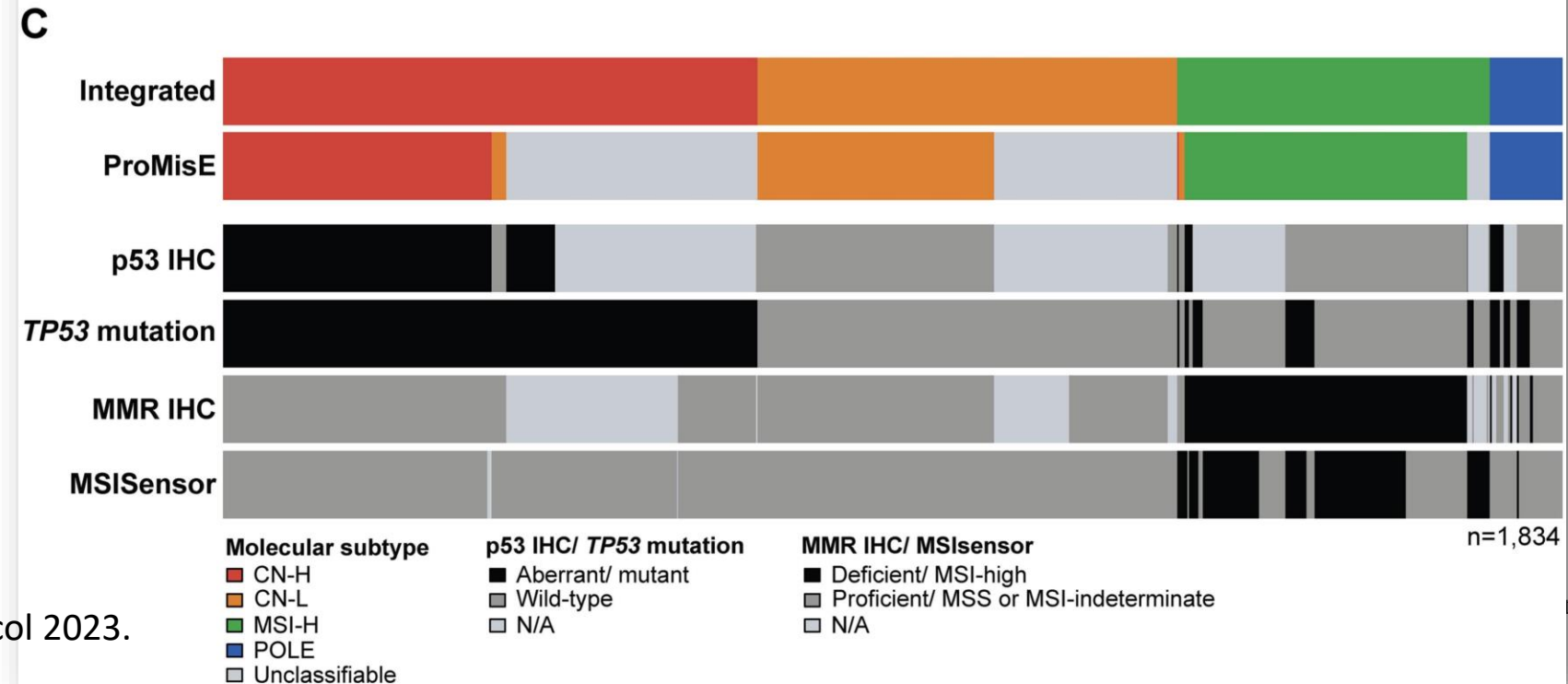
Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center

5.9% of P53 WD by IHC are CN-H



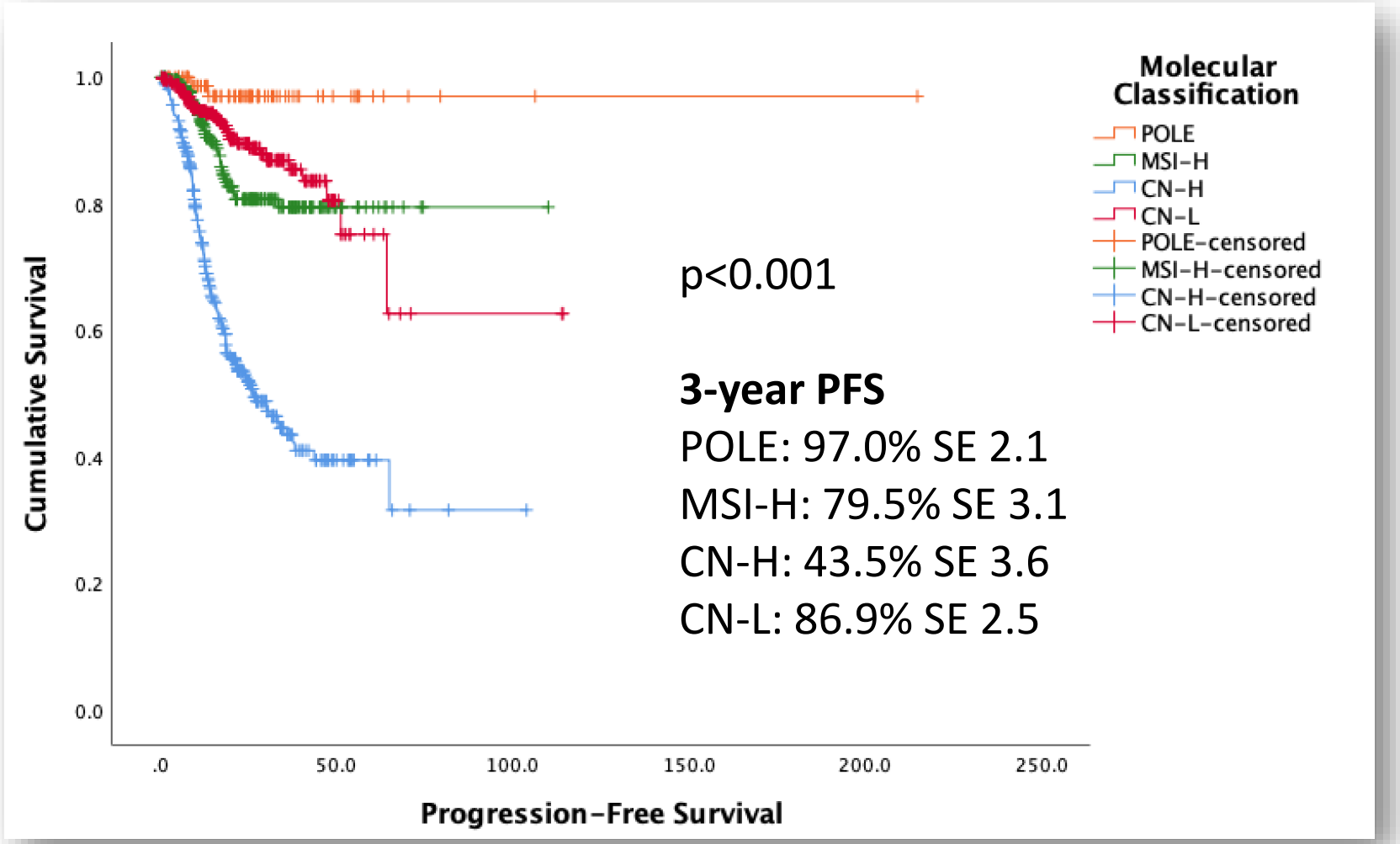
5.7% of MMR-p by IHC are MSI-H



Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023.

n Kettering

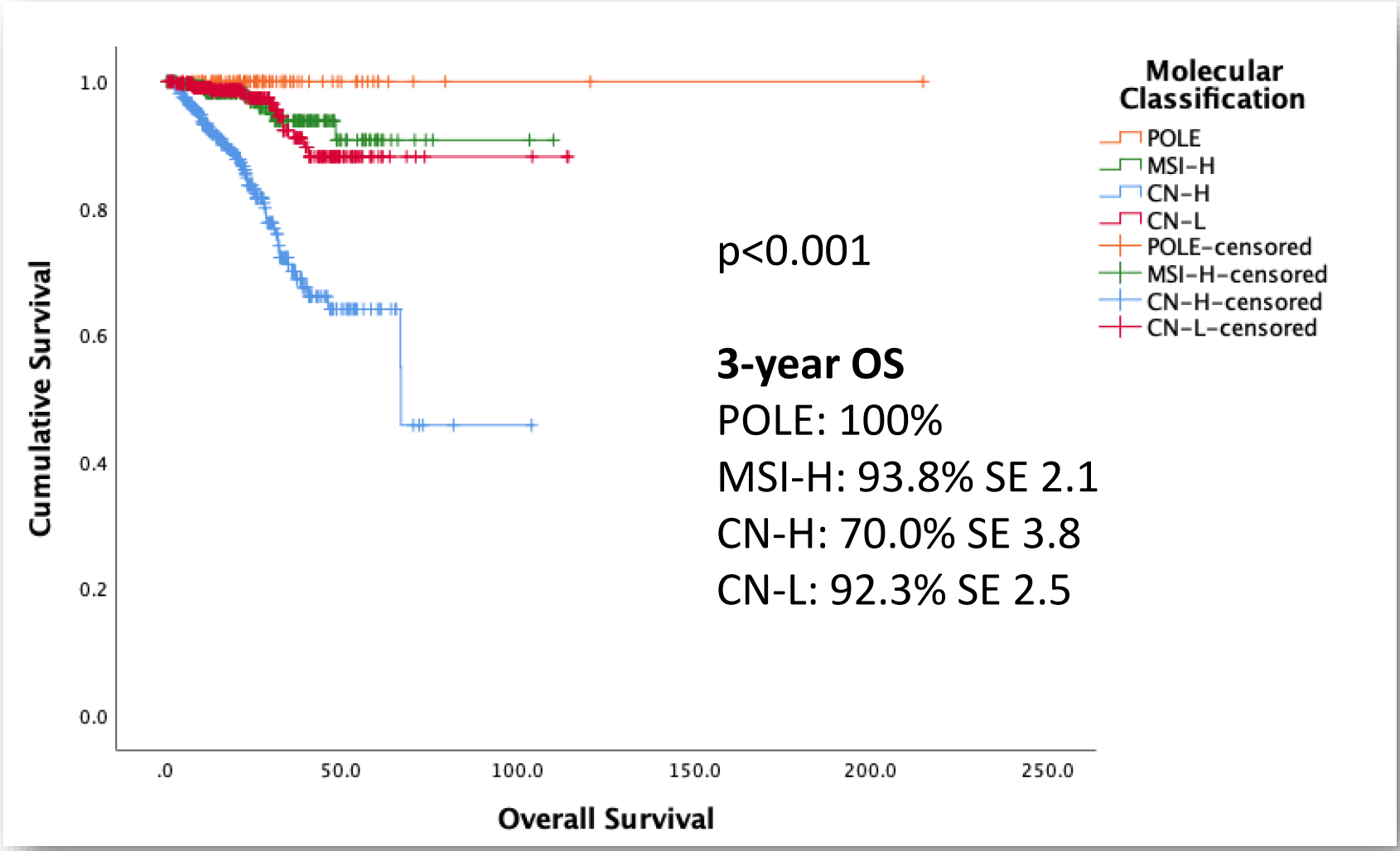
Progression-Free Survival



Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center

Overall Survival



Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

Memorial Sloan Kettering Cancer Center

MSK Experience

- Largest single-institution series of endometrial cancer molecular classification with integration of IHC and molecular data
- CN-H is an independent predictor of progression-free survival
- Our patient population is mostly CN-H molecular subtype, likely reflective of the referral-based nature of our institution
- There is a high level of histology heterogeneity to consider amongst molecular subtypes

Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

As of May 22, 2023

- In cBioPortal, there are **3,442** endometrial cancer samples (some patients have more than one sample IMPACTed).

- Of these, **2,654** (77%) are primary tumors.

Clinical Utility of Prospective Molecular Characterization in Advanced Endometrial Cancer

- To understand whether prospective molecular characterization of recurrent and metastatic disease can facilitate enrollment onto clinical trials.
- Experimental design: MSK-IMPACT from 189 patients treated at MSKCC.
- **Results: Of the 68% of patients harboring potentially actionable mutations, 27% were enrolled to matched clinical trials, of which 47% achieved clinical benefit.**
- **Conclusions:** Prospective clinical sequencing of advanced endometrial cancer helps treatment decision making by detecting microsatellite status, germline predisposition syndromes, and actionable mutations. A proportion of patients tested received investigational, genomically matched therapy as part of clinical trial.

Soumerai T, et al. (MSKCC) Clin Cancer Res 2018

Clinical outcomes of patients with POLE mutated endometrioid endometrial cancer

- 23 Patients with endometrioid endometrial cancer harboring somatic POLE exonuclease domain mutations (EDM).
- 20 primary and 3 recurrent tumors sequenced.
- 19 (83%) were stage I/II and 4 (17%) were stages III/IV.
- 13 (57%) were of FIGO grades 1/2, 10 (43%) grade 3.
- All patients were treated with surgery and 17 (89%) received adjuvant therapy.
- After median follow-up of 30 months, 4 developed recurrences: 3 with initial grade 3 stage I and 1 with grade 1 stage III disease. One patient with grade 2 stage IV EEC had progressive disease after treatment.
- metastatic disease and recurrences in initially uterine-confined cases were observed.
- Further research is warranted before incorporating the presence of POLE EDM into decision-making regarding adjuvant therapy.

Stasenko M, et al. (MSKCC) Gynecol Oncol 2020

Genetic and molecular subtype heterogeneity in **newly diagnosed** early- and advanced-stage endometrial cancer

- To characterize the molecular profiles of prospectively-accrued newly-diagnosed early and advanced-stage endometrial cancers (ECs).
- 175 ECs of 7 histologic types (n = 135 FIGO stages I/II, n = 40 FIGO stages III/IV).
- Irrespective of histologic type, all 175 ECs could be stratified into the molecular subtypes
  - 49 (28%) MMR-deficient
  - 39 (22%) p53 abnormal
  - 12 (7%) POLE molecular subtypes
  - 75 (43%) p53 wild-type
- **Advanced-stage endometrioid had a higher fraction of genome altered** (0.1% vs. 12%, $p < 0.001$) **and ARID1B mutations** (0% vs. 11%, $p = 0.01$).
- **Advanced-stage serous had more frequent ERBB2 amplification (18% vs. 8%) and PIK3CA mutations (46% vs. 27%).**
- Study demonstrated the molecular heterogeneity within and across histologic types of EC and the increased genomic complexity of advanced-stage ECs.

Da Cruz Paula A, et al. (MSKCC) Gynecol Oncol 2021

Memorial Sloan Kettering Cancer Center

Clinicopathologic and Genomic Analysis of *TP53*-Mutated Endometrial Carcinomas

- *185 TP53*-mutant tumors lacking microsatellite instability or pathogenic *POLE* mutations, treated at MSK
- *TP53*-mutated endometrial ca encompassed:
  - Serous (*n* = 102, 55.1%)
  - High-grade endometrial with ambiguous features/not otherwise specified (*n* = 44, 23.8%)
  - Endometrioid of all grades (*n* = 28, 15.1%)
  - Clear cell ca (*n* = 11, 5.9%).
- ***ERBB2* amplification was present across *TP53*-mutated histotypes (8%-19%).**
- Although overall survival was similar across histologic types, serous carcinomas presented more frequently at stage IV, had more persistent/recurrent disease, and reduced disease-free survival.

- *TP53*-mutated endometrial carcinomas display clinical and molecular similarities across histologic subtypes. **Our data provides evidence to suggest performance of *ERBB2* assessment in all *TP53*-mutated endometrial carcinomas**. Given the distinct clinical features of serous carcinomas, histologic classification continues to be relevant.

Momeni-Boroujeni A, et al. (MSKCC) Clin Cancer Res 2021

Memorial Sloan Kettering Cancer Center

Genomic landscape of endometrial carcinomas of no specific molecular profile (NSMP)

- Copy number-low Endometrial ca (NSMP) have a prognosis intermediate between POLE-mutated and copy number-high.
- We identified **472 NSMP-EC**:
  - Molecular Cluster 1 NSMP tumors with PTEN and PIK3R1 mutations (best outcome)
  - Molecular Cluster 2 NSMP tumors with PTEN and PIK3CA mutations
  - **Molecular Cluster 3 NSMP lack of PTEN mutations with chromosome 1q high-level gain (poor)**
- 73% of non-endometrioid NSMP-ECs mapped to Cluster 3.
- **Cluster 3 were more Grade 3 (30%), Estrogen Receptor-negative/weak (54.5%) and FIGO stages III or IV.**
- Molecular cluster 3 tumors had the worst survival and C1 tumors had the best outcome.
- NSMP-ECs are a heterogenous group of tumors and comprise both aggressive and low-risk ECs that can be identified based on mutation and copy number data.

Momeni-Boroujeni A, et al. (MSKCC) Mod Pathol 2022

Germline Drivers in Endometrial Cancer

- Of 1625 unselected patients with EC, **216 (13%) had germline pathogenic variants.**
- With 63% of germline pathogenic variants in high-penetrance genes (MMR and homologous recombination) exhibiting biallelic inactivation, potentially driving cancer development.
- This supports germline assessment in EC given implications for treatment and cancer prevention.

Gordhandas S. et al. (MSKCC) JNCI 2023

Germline Drivers of Gynecologic Carcinosarcomas

- Of 216 patients, 167 (77%) had endometrial carcinosarcoma and 49 (23%) ovarian carcinosarcoma.
- **In endometrial carcinosarcoma, germline pathogenic variants were found in 19 (11%) of 167 patients.**
- **In ovarian carcinosarcoma, germline pathogenic variants were found in 10 (20%) of 49 patients.**
- Our data supports germline testing for patients with gynecologic carcinosarcomas, given implications for treatment and risk-reduction in patients and at-risk family members.

Sia T, et al. (MSKCC) Gynecol Oncol 2023

Conclusions

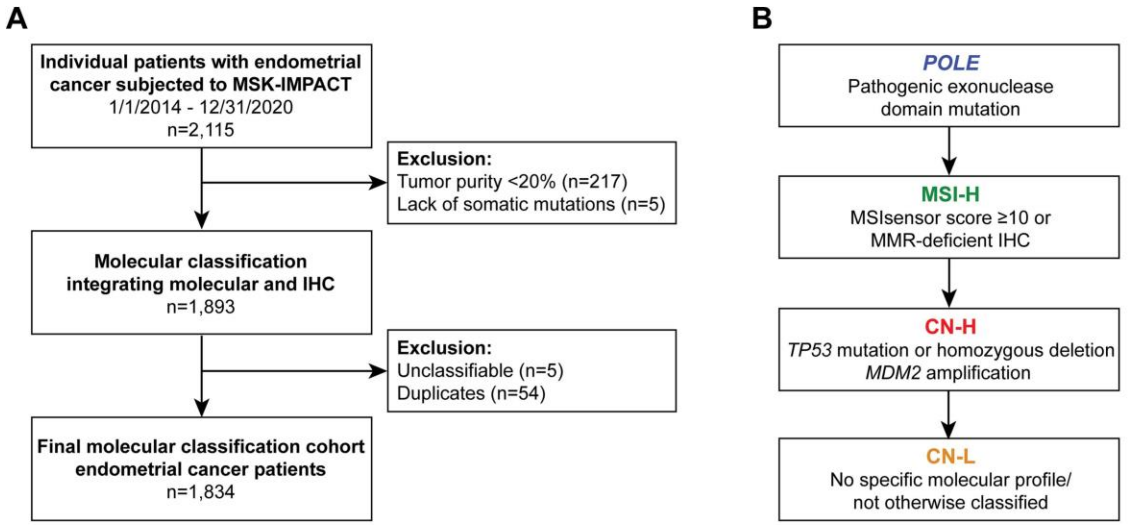
- Endometrial cancer remains an understudied disease.
- Moving from histotyping alone to combined histotyping and molecular classification is needed.
- Molecular classification is feasible and improves diagnostic classification and provides prognostic information and will likely guide therapy.
- The combination of histotype, surgical staging, and molecular profiling will help guide de-escalation strategies and trials and direct escalation of adjuvant therapy when otherwise may not have been offered.

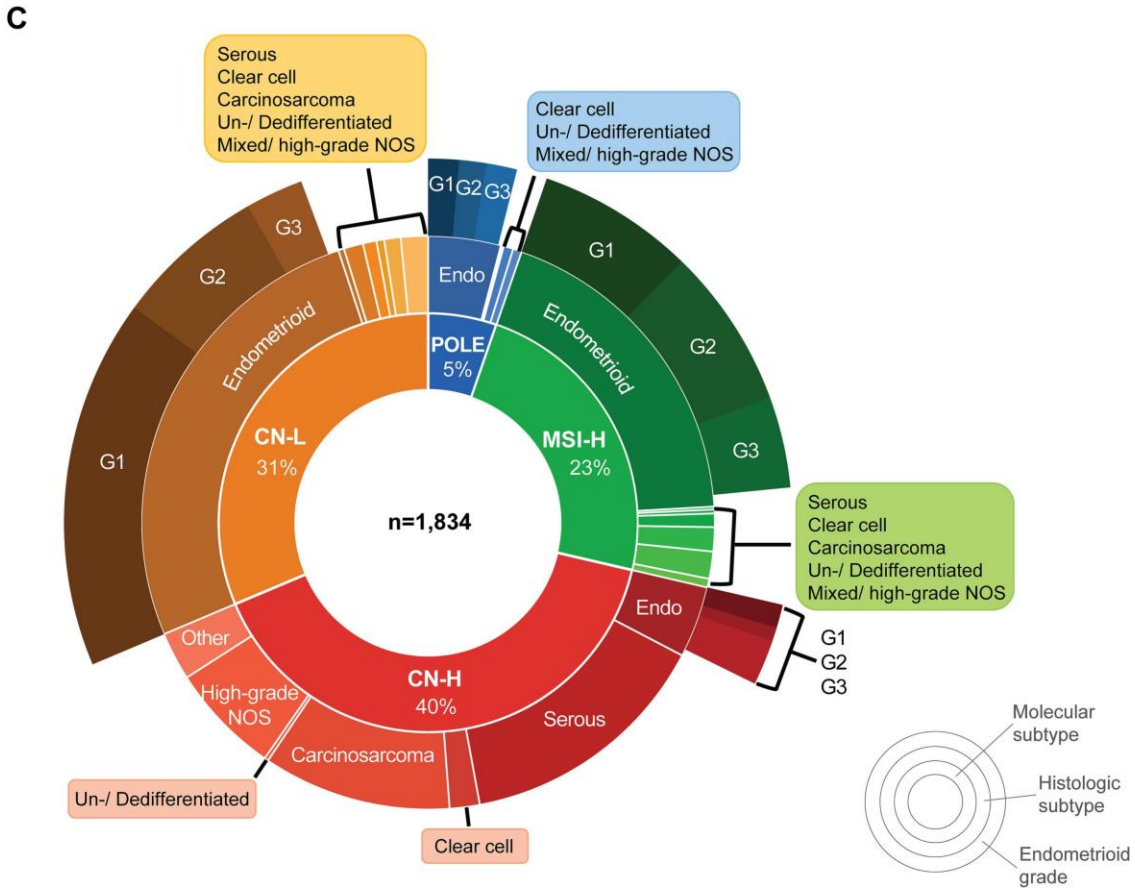
Conclusions

- Endometrial cancer remains an understudied disease.
- Moving from histotyping alone to combined histotyping and molecular classification is needed.
- Molecular classification is feasible and improves diagnostic classification and provides prognostic information and will likely guide therapy.
- The combination of histotype, surgical staging, and molecular profiling will help guide de-escalation strategies and trials and direct escalation of adjuvant therapy when otherwise may not have been offered.

Thank You

Memorial Sloan Kettering Cancer Center™





Memorial Sloan Kettering Cancer Center

Thank you

NSGO