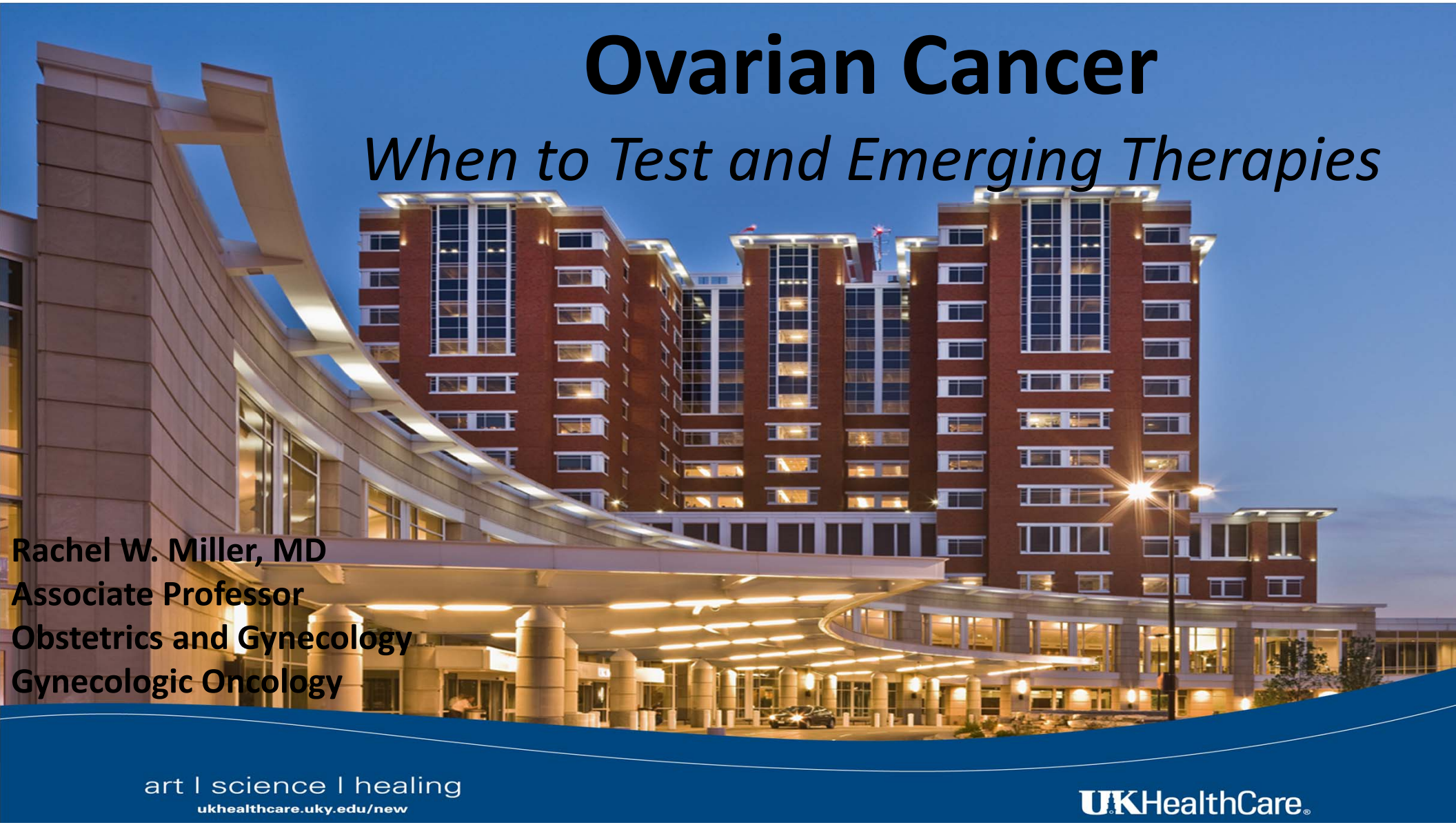
Ovarian Cancer

When to Test and Emerging Therapies



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art | science | healing
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Faculty Disclosure

No financial interests to disclose.

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Educational Need/Practice Gap

Gap = Gynecologic cancers, especially ovarian cancer, have a high mortality rate when treated with conventional, non-targeted cytotoxic chemotherapy treatments.

Need = A greater understanding of novel treatment options, but especially targeted therapies for the treatment of advanced gynecologic cancers, represent a major unmet educational need.

Objectives

Upon completion of this educational activity, you will understand the diagnostic, prognostic, and therapeutic applications of comprehensive genomic profiling in ovarian cancer.

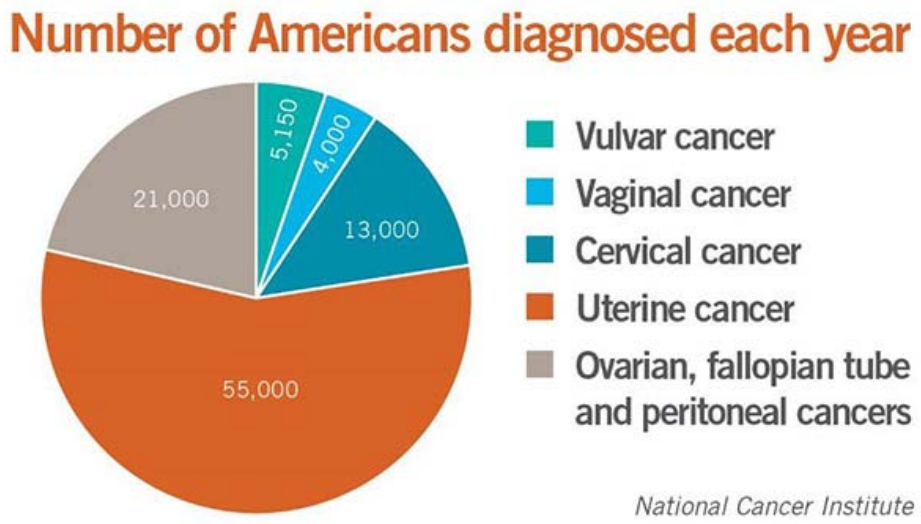
Expected Outcome

Providers will understand the role of comprehensive genomic profiling in ovarian cancer and recommendations according to National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology.

Comprehensive Genomic Profiling in Gynecologic Cancer

In 2018:

- 110,000 new cases
- 32,000 deaths



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Cancer Statistics, 2018
Siegel et al.
CA CANCER J CLIN 2018;68:7–30

Epithelial Ovarian Cancer

- Leading cause of death from gynecologic cancer in the US
- In 2018, it is estimated that
  - 22,240 new diagnoses
  - 14,070 deaths
- Fifth most common cause of cancer death

Estimated Deaths

Females		
Lung & bronchus	70,500	25%
Breast	40,920	14%
Colon & rectum	23,240	8%
Pancreas	21,310	7%
Ovary	14,070	5%
Uterine corpus	11,350	4%
Leukemia	10,100	4%
Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	7,340	3%
All Sites	**286,010**	**100%**

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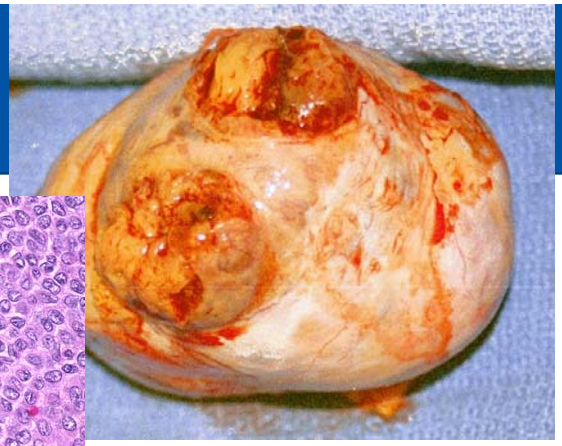
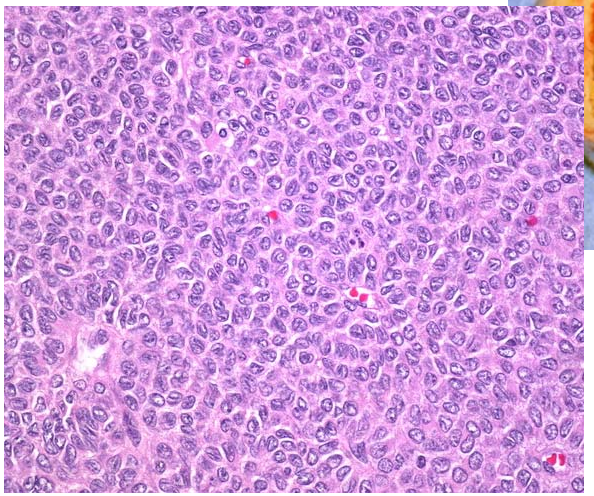
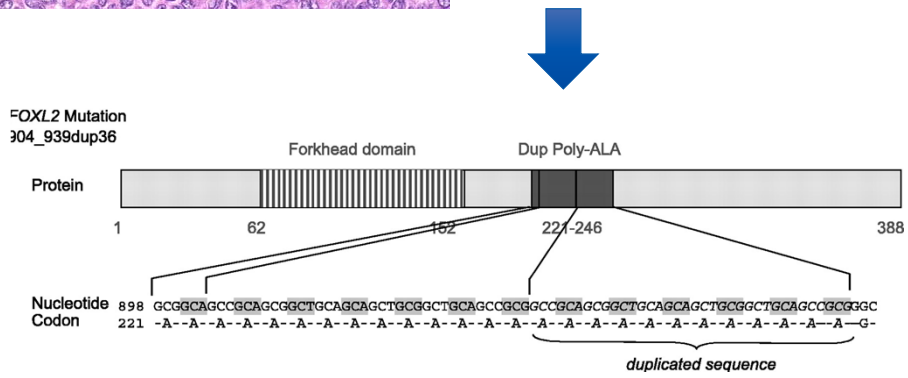
CA CANCER J CLIN 2018;68:7–30

Diagnostic Applications of CGP





- FOXL2 in adult granulosa cell tumors
  - 19% of tumors misdiagnosed
  - accounted for 72% of disease-related deaths
- SMARCA4 in ovarian small cell carcinoma
- DICER1 in Sertoli-Leydig cell tumors
- Absence of TP53 in low grade serous ovarian cancer



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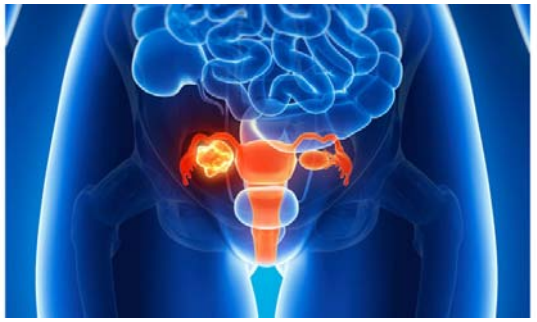
Bryk S, Farkkila A, Butzow R, et al. Characteristics and outcome of recurrence in molecularly defined adult-type ovarian granulosa cell tumors. Gynecol Oncol 2016; 143:571–577.

Prognostic Applications – Ovarian Cancer

- Low grade serous ovarian cancer
  - BRAF mutations are associated with much better prognosis than mutations in KRAS
- High grade serous ovarian cancer
  - BRCA1 or 2 mutations associated with longer OS and increased sensitivity to platinum
  - CCNE1 gene amplification is a marker of worse OS and primary platinum resistance



Therapeutic Applications

	Clinically relevant genomic alteration	Potential targeted therapies[a]
Ovarian	*BRCA1/2*	PARP inhibitors
	KRAS	MEK inhibitors
	FGFR2	FGFR inhibitors
	POLE ultramutator	Anti-PD1 immune check-point inhibitors
	MSI-high	Anti-PD1 immune check-point inhibitors
	ERBB2	HER2-targeting monoclonal antibody
Cervical	*PIK3CA*	PI3K inhibitors, mTOR inhibitors, AKT inhibitors
	EGFR (SCC)	Anti-EGFR targeted therapy
	PTEN	PI3K inhibitors, mTOR inhibitors, AKT inhibitors
	STK11	mTOR inhibitors
	KRAS (adenocarcinoma)	MEK inhibitors

Only FDA-approved in Gynecologic Cancer:

- PARPi
- Pembrolizumab

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Genomic profiling of gynecologic cancers and implications for clinical practice.
Prendergast, Emily; Elvin, Julia
Current Opinion in Obstetrics & Gynecology. 29(1):18-25, February 2017.

Therapeutic Applications - Ovarian Cancer

Mutation	Therapy
BRCA 1 / 2	PARP inhibitors
KRAS	MEK inhibitors
BRAF	MEK, BRAF inhibitors
ERBB2	HER2/HER3 antibodies, EGFR inhibitors
ARID1A (clear cell)	PI3K, AKT, mTOR inhibitors
NF1	MEK inhibitors
CCND1, CCNE1, CDK4 mutations, CCND2 (amplification)	CDK 4/6 inhibitors

Genomic profiling of gynecologic cancers and implications for clinical practice.
Prendergast, Emily; Elvin, Julia
Current Opinion in Obstetrics & Gynecology. 29(1):18-25, February 2017.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2018
Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer & Less Common Histopathologies

RECURRENT DISEASE[v]

Rising CA-125, no previous chemotherapy or Clinical relapse, no previous chemotherapy	→	• Imaging studies as clinically indicated:[e,w] Chest/abdominal/pelvic CT, MRI, PET/CT, or PET • Tumor molecular testing[x]
Clinical relapse, previous chemotherapy	→	• Imaging studies as clinically indicated:[e,w] Chest/abdominal/pelvic CT, MRI, PET/CT, or PET • Tumor molecular testing[x]
Serially rising CA-125, previous chemotherapy	→	• Imaging studies as clinically indicated:[e,w] Chest/abdominal/pelvic CT, MRI, PET/CT, or PET • Tumor molecular testing[x]

- Validated molecular testing should be performed in a CLIA-approved facility
- Testing should include at least:
  - BRCA1/2,
  - homologous recombination pathway genes, and
  - microsatellite instability or DNA mismatch repair

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NCCN Guidelines Version 2.2018
Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer & Less Common Histopathologies

Principles of Systemic Therapy

	Cytotoxic Therapy (In alphabetical order)*		Targeted Therapy*
Preferred Agents	**Platinum-Sensitive Disease**[l,m] Carboplatin/gemcitabine[2] Carboplatin/gemcitabine/bevacizumab[n,o,p,3] Carboplatin/liposomal doxorubicin[4] Carboplatin/paclitaxel[5] Carboplatin/paclitaxel/bevacizumab[l,n,o,p,6] Cisplatin/gemcitabine[7]	**Platinum-Resistant Disease** Docetaxel[8] Etoposide, oral[9] Gemcitabine[10,11] Liposomal doxorubicin[10,11] Liposomal doxorubicin/bevacizumab[n,o,12] Paclitaxel (weekly)[13] ± pazopanib[14] Paclitaxel (weekly)/bevacizumab[n,o,12] Topotecan[15,16] Topotecan/bevacizumab[n,o,12]	**Single Agents** Bevacizumab[n,o,17,18] Olaparib[q,19] Rucaparib[r,20]

Olaparib

- Deleterious germline BRCA-mutated
- Treated with three or more lines of chemotherapy
- Response rate 34% response rate
- Median response duration of 7.9 months

Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244-250

Rucaparib

- Deleterious germline and/or somatic BRCA-mutated
- Treated with two or more lines of chemotherapy
- Patients with somatic mutations had same objective response rate (85%) and progression free interval (12.8 months) as patients with germline mutations

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Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017;18:75-87

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This is the FDA's first tissue/site-agnostic approval.

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Principles of Systemic Therapy

	Regimens (In alphabetical order)[a,l]	Recommended Use
Useful in Certain Circumstances	5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[n,o]	Mucinous carcinoma
	Capecitabine + oxaliplatin ± bevacizumab (category 2B for bevacizumab)[n,o]	Mucinous carcinoma
	Carboplatin/paclitaxel, albumin bound (platinum-sensitive disease)	Paclitaxel, albumin bound may be substituted for taxane for confirmed hypersensitivity
	Carboplatin/paclitaxel[t]	Elderly patients (> age 70) with platinum-sensitive disease
	Pembrolizumab[25]	Microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors[u]

Varga A, Piha-Paul SA, Ott PA, et al. Pembrolizumab in patients (pts) with PD-L1–positive (PD-L1+) advanced ovarian cancer: Updated analysis of KEYNOTE-028 [abstract]. J Clin Oncol 2017;35: Abstract 5513

Principles of Systemic Therapy

	Regimens[a]	Recommended Use
Useful in certain circumstances	Pazopanib[y] (category 3)	Single-agent maintenance therapy if complete clinical remission following primary therapy for stage II-IV disease, if no prior bevacizumab
	Bevacizumab[n,o]	May be continued as a single-agent maintenance therapy if used previously as part of a combination therapy, if partial or complete remission following: • Primary therapy for stage II-IV disease; or • Recurrence therapy for platinum-sensitive disease
	Niraparib[x]	Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy
	Olaparib[x]	Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy
	Rucaparib[x]	Single-agent maintenance therapy if platinum-sensitive disease with partial or complete response following two or more lines of platinum-based therapy

Use of comprehensive genomic profiling to direct point-of-care management of patients with gynecologic cancers

Gynecologic Oncology 141 (2016) 2–9

Lorna Rodriguez-Rodriguez, Kim M. Hirshfield, Veronica Rojas, Robert S. DiPaola, Darlene Gibbon, Mira Hellmann, Sara Isani, Aliza Leiser, Gregory M. Riedlinger, Allison Wagreich, Siraj M. Ali, Julia A. Elvin, Vincent A. Miller, Shridar Ganesan

- 69 patients with gynecologic cancers
- Prospective trial at Rutgers CINJ - genomic profiling of patients with rare or refractory cancers
- Tumor specimens underwent CGP in commercial lab
- All classes of genomic alterations were assessed
- MTB review with consensus recommendations

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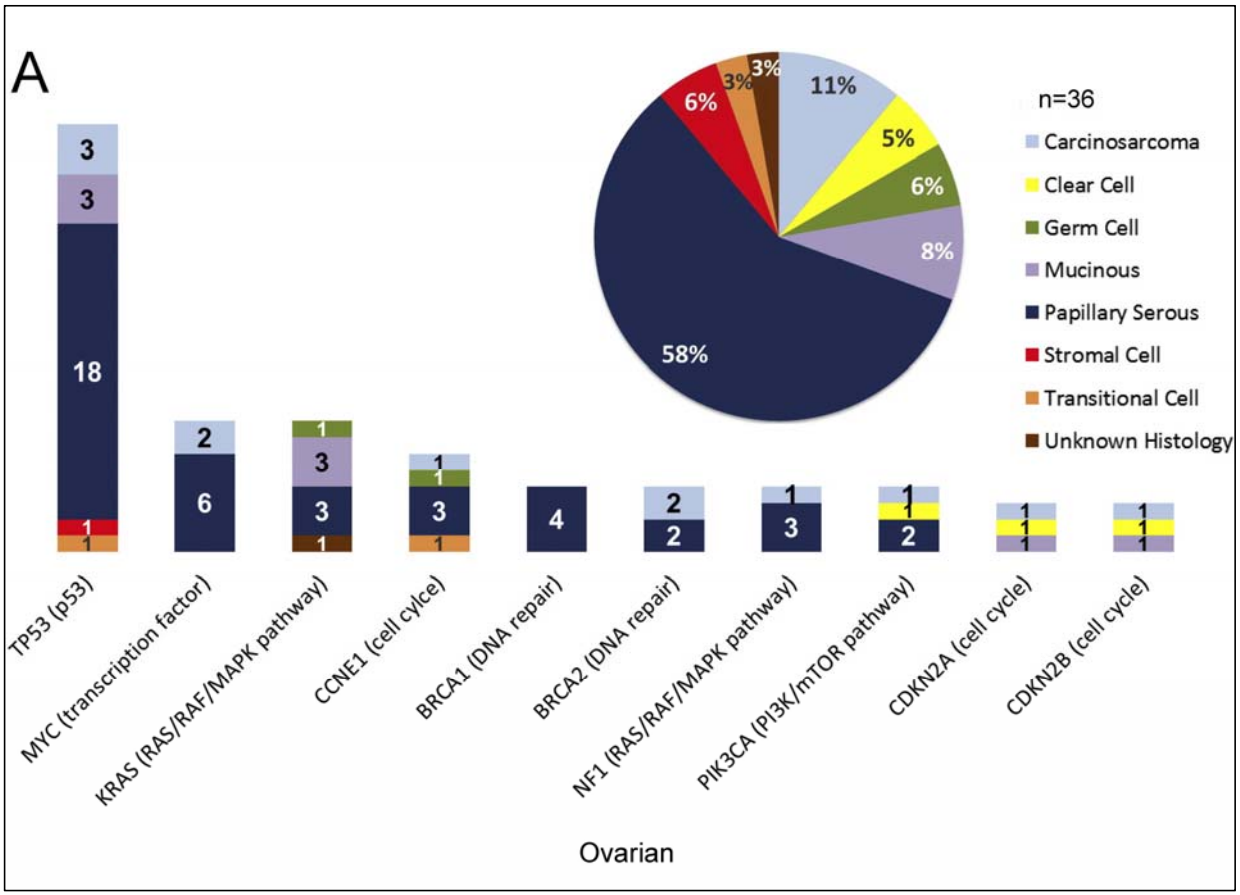
Tumor histological subtypes and most common mutations – Ovarian Cancer



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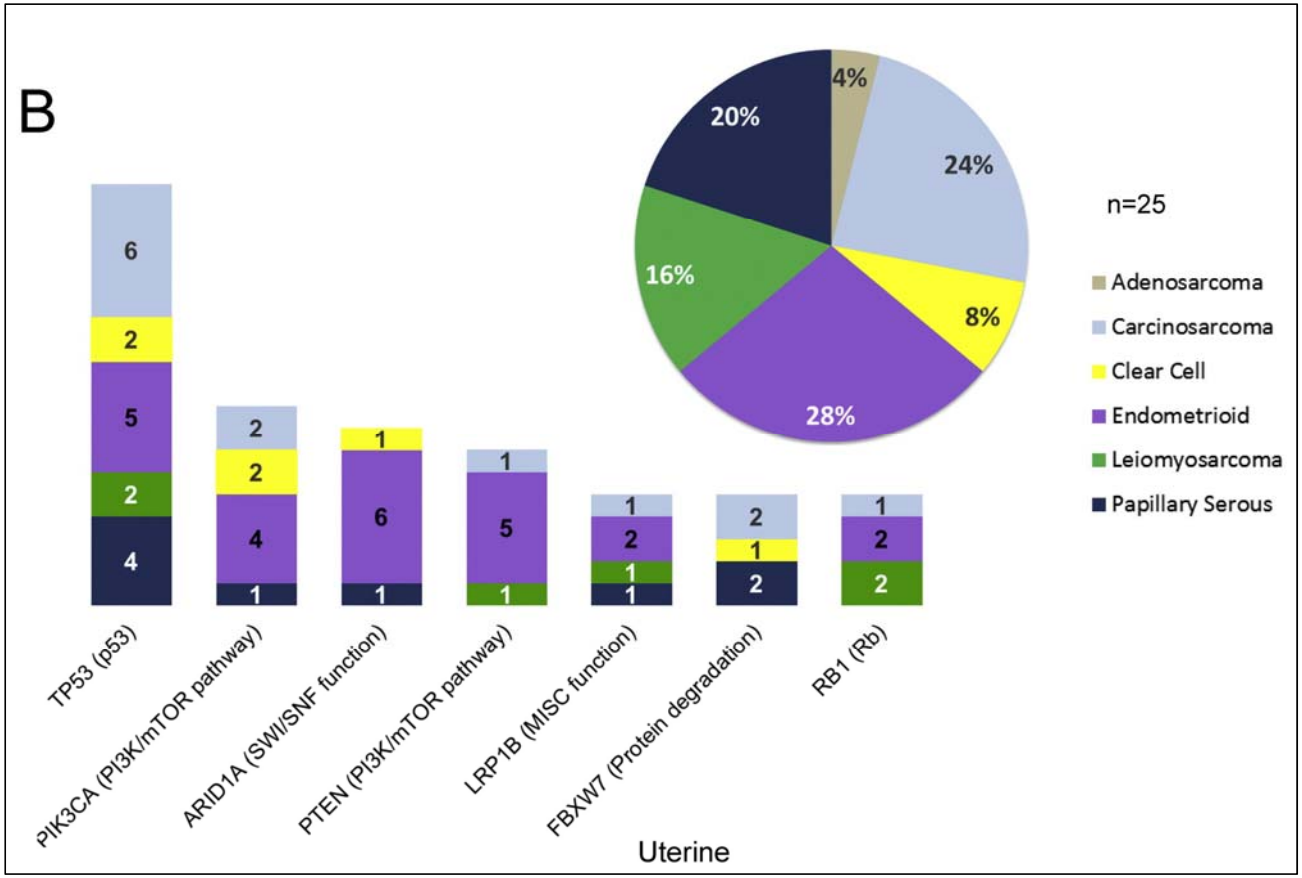
Rodriguez-Rodriguez et al.Gynecologic Oncology. 141(1):2-9, April 2016.

Tumor histological subtypes and most common mutations – Uterine Cancer



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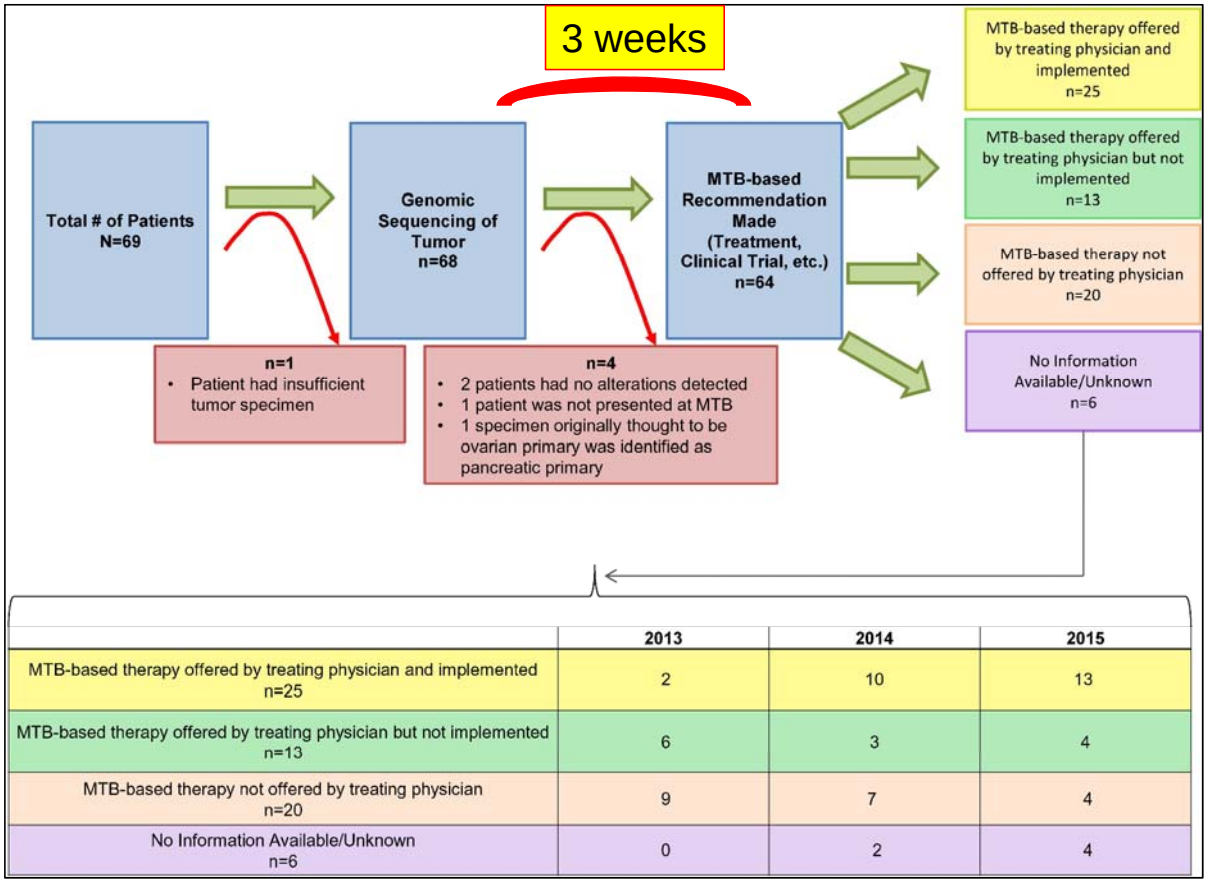

	2013	2014	2015
MTB-based therapy offered by treating physician and implemented n=25	2	10	13
MTB-based therapy offered by treating physician but not implemented n=13	6	3	4
MTB-based therapy not offered by treating physician n=20	9	7	4
No Information Available/Unknown n=6	0	2	4

93% (64/69)
had one or more clinically relevant genomic alterations

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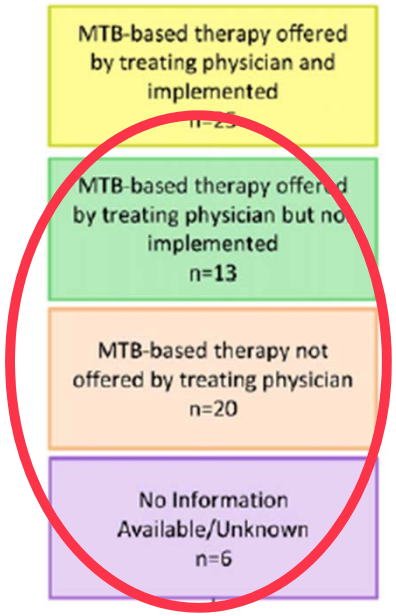
Rodriguez-Rodriguez et al.Gynecologic Oncology. 141(1):2-9, April 2016.

Reasons for not receiving treatment:



- no evidence of disease/no advantage of adjuvant targeted therapy
- deteriorating performance status
- death
- lost to follow-up
- patient refusal
- drug could not be obtained
- drug contraindicated
- treating physician opted for a different treatment

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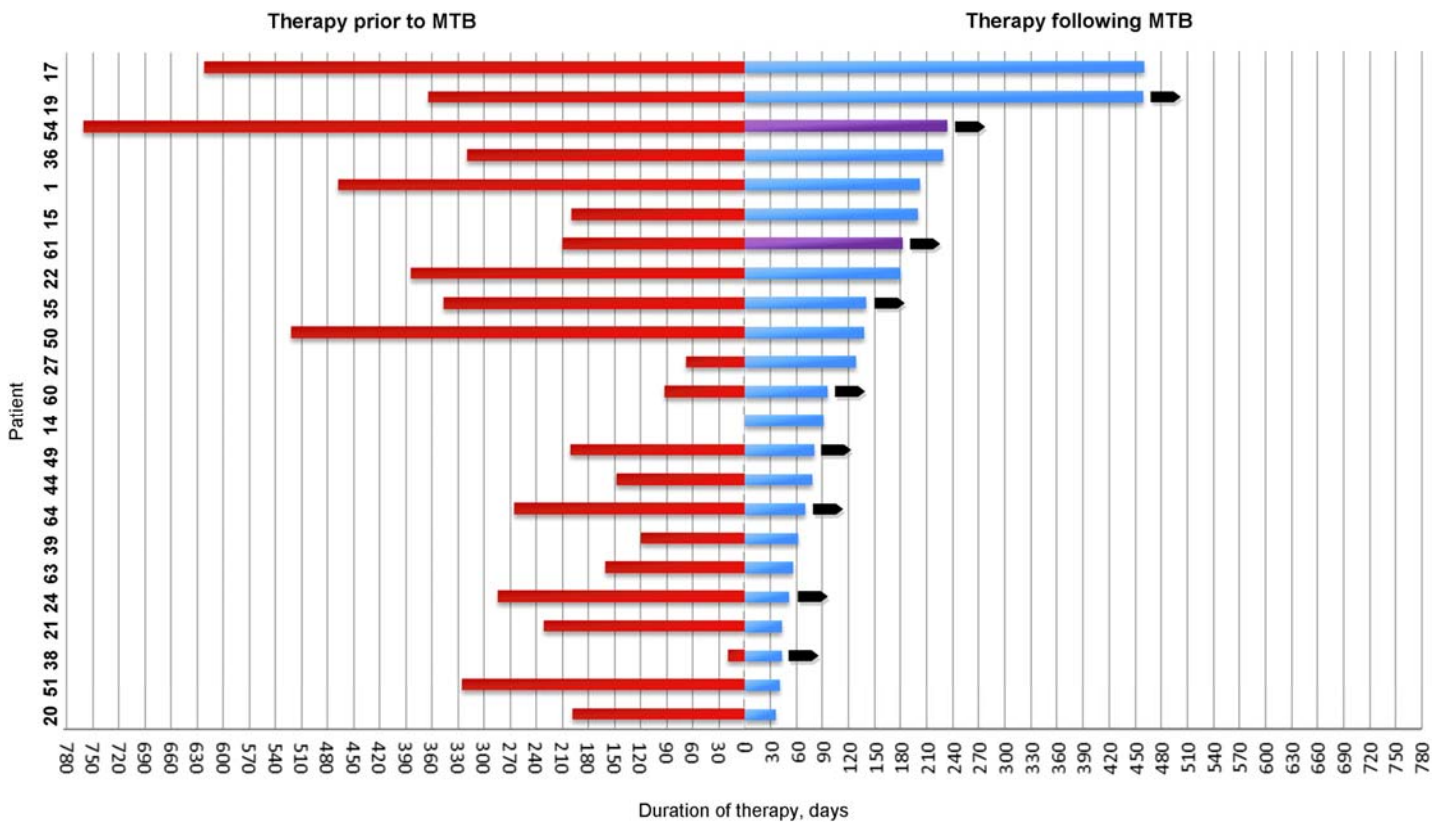
Rodriguez-Rodriguez et al.Gynecologic Oncology. 141(1):2-9, April 2016.

Clinical Utility

- MTB-based recommendations were implemented in 25 patients
  - mTOR inhibitor with or without an aromatase inhibitor in PIK3CA or PI3K pathway mutations (endometrial cancer)
  - MEK inhibitor in KRAS mutations (endometrial cancer)
  - platinum-based chemotherapy
    - BRCA2 mutations
  - radiation therapy
    - ATM mutations
- At least one clinical trial for 40 of the 64 patients (63%)
  - 12% (n = 3) were treated in the setting of a clinical trial

Rodriguez-Rodriguez et al.Gynecologic Oncology. 141(1):2-9, April 2016.

Progression-free survival



64% of patients had complete or partial response, stable disease, or clinical benefit

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Rodriguez-Rodriguez et al.Gynecologic Oncology. 141(1):2-9, April 2016.

Use of comprehensive genomic profiling to direct point-of-care management of patients with gynecologic cancers

Gynecologic Oncology 141 (2016) 2–9

"This current proof-of-concept study shows that with a well-trained expert team, point-of-care management of gynecologic testing is feasible and patient benefit can be attained, supporting the need for further studies and guidelines on clinical decision making with greater availability of broad genomically based diagnostics."

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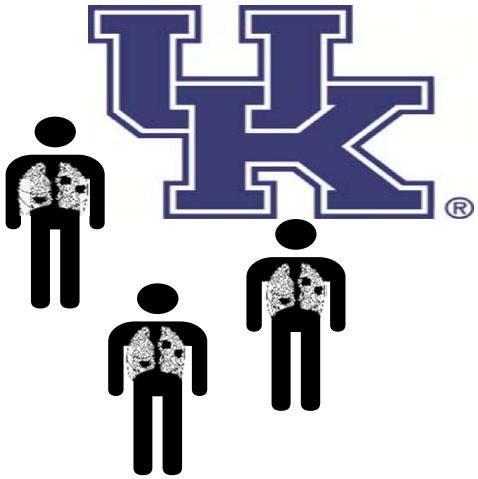
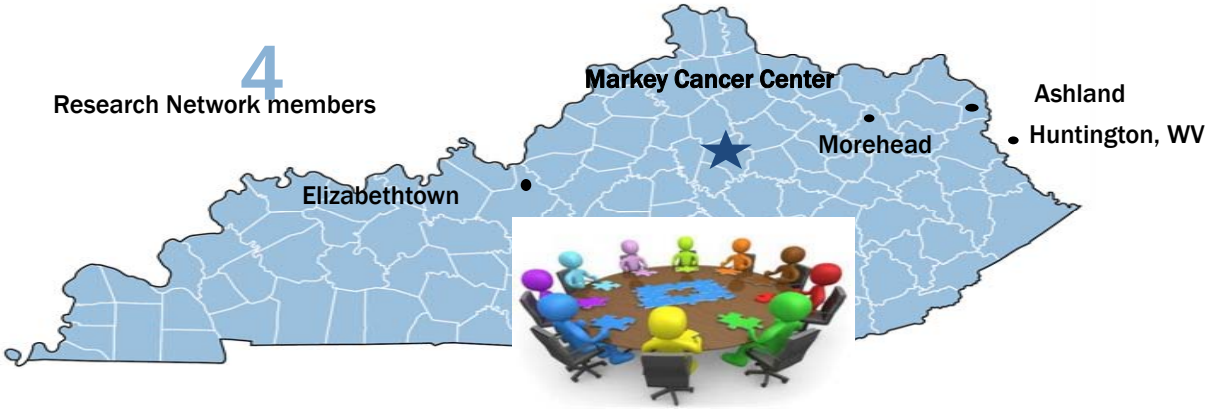
The Markey Cancer Center Molecular Tumor Board





Genomic Report:

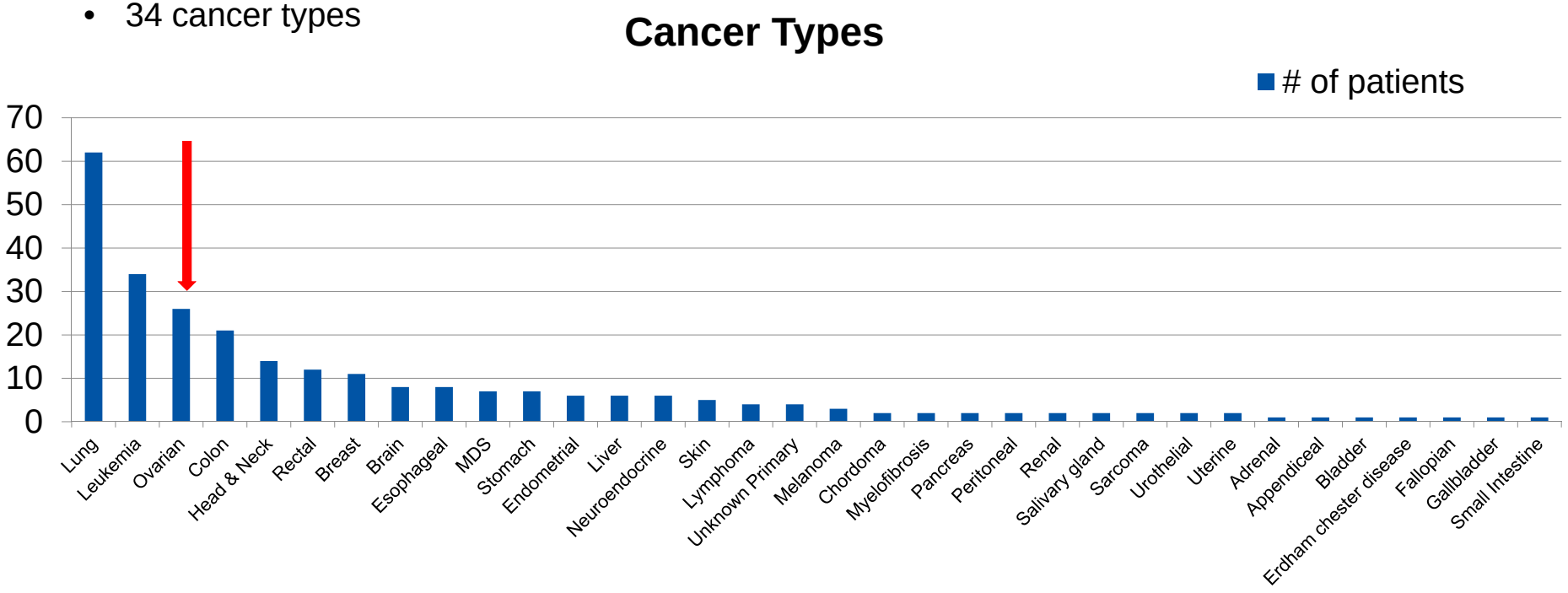
Gene 1 – mutation detected
Gene 2
Gene 3 – mutation detected
Gene 4

PMMTB Recommendations:

1. Clinical trial
2. Off-label treatment
3. Standard treatment (not targeted)

MTB Patient Statistics

- 256 Patients
  - 34 cancer types



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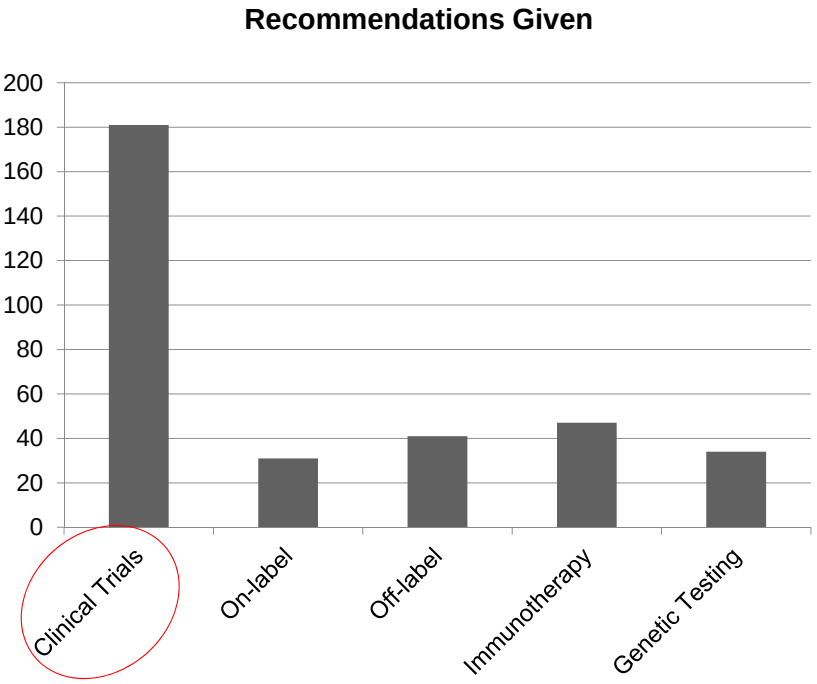
MTB Patient Reviews

- **First meeting occurred on December 20, 2016**
- **24 meetings** thus far
- **96 patient cases presented**
  - UK: 75
  - TJ Samson: 7
  - Owensboro: 4
  - KentuckyOne Health: 3
  - The Medical Center – Bowling Green: 2
  - Baptist Health: 1
  - Hardin Memorial: 1
  - Highlands Regional: 1
  - King's Daughter's: 1
  - Tug Valley ARH: 1
- **160 UK patient cases reviewed (genomics only)**

Total cases reviewed by MTB : 256



*Note: more than one option is recommended per patient

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Precision Medicine Clinic (PMC) for Patients

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