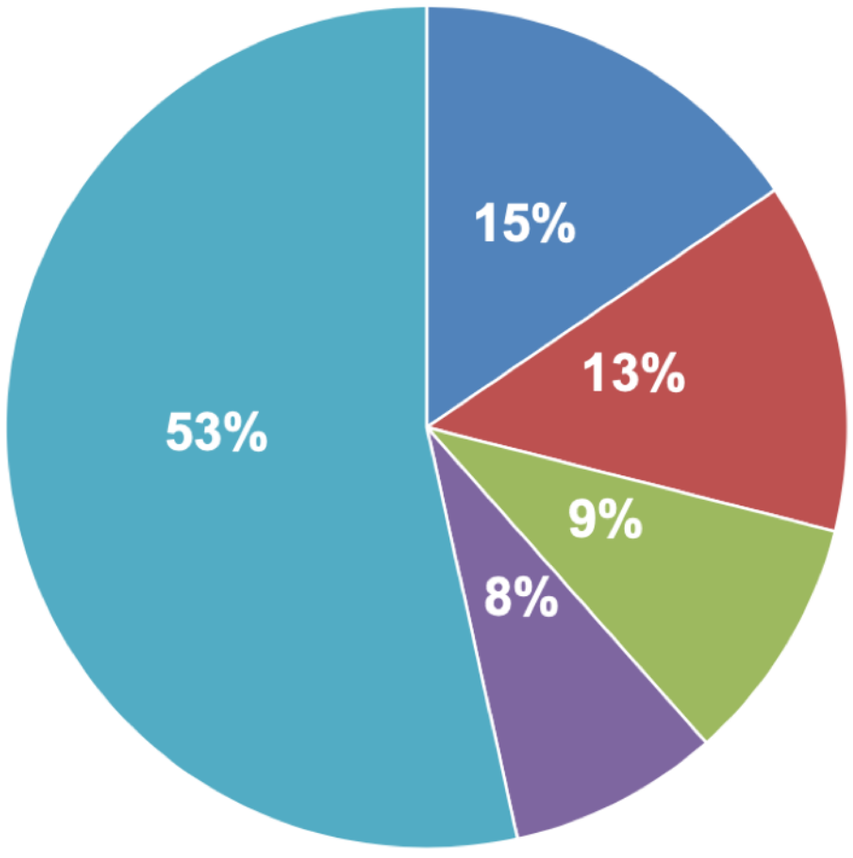
# Whats new in Colon Cancer and Pancreatic cancer in 2021

Warren Brenner M.D

# At a Glance

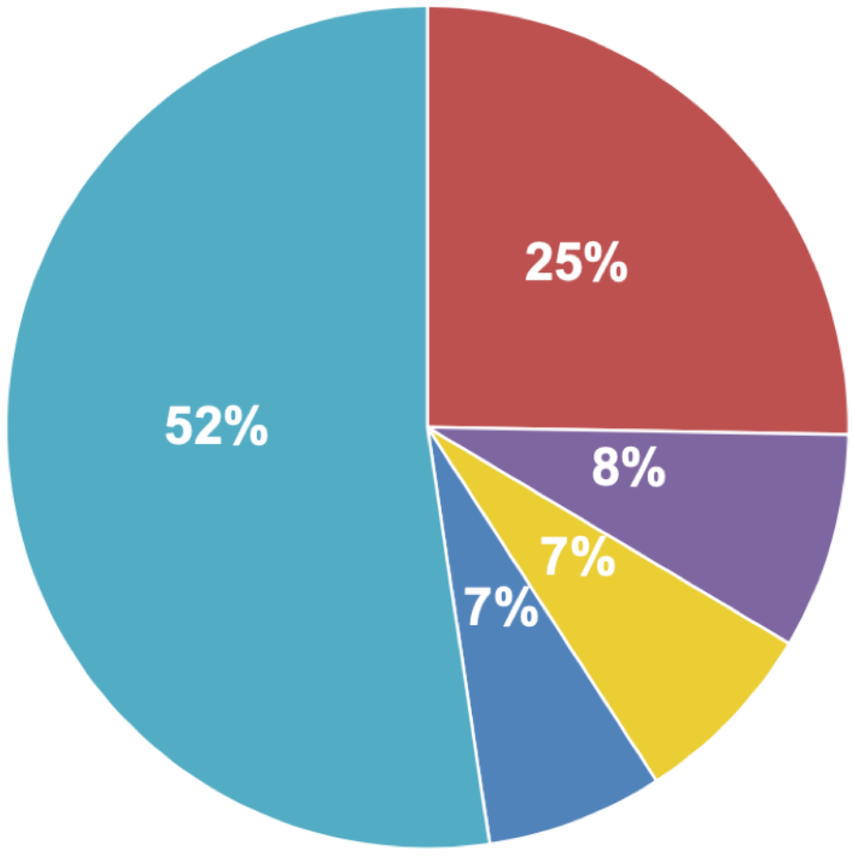
Breast, lung and bronchus, prostate, and colorectal cancers account for almost 50% of all new cancer cases in the United States. Lung and bronchus, colorectal, pancreatic, and breast cancers are responsible for nearly 50% of all deaths.

### New Cancer Cases, 2018




- Breast: 268,670
- Lung and bronchus: 234,030
- Prostate: 164,690
- Colon and rectum: 140,250
- Other: 927,710

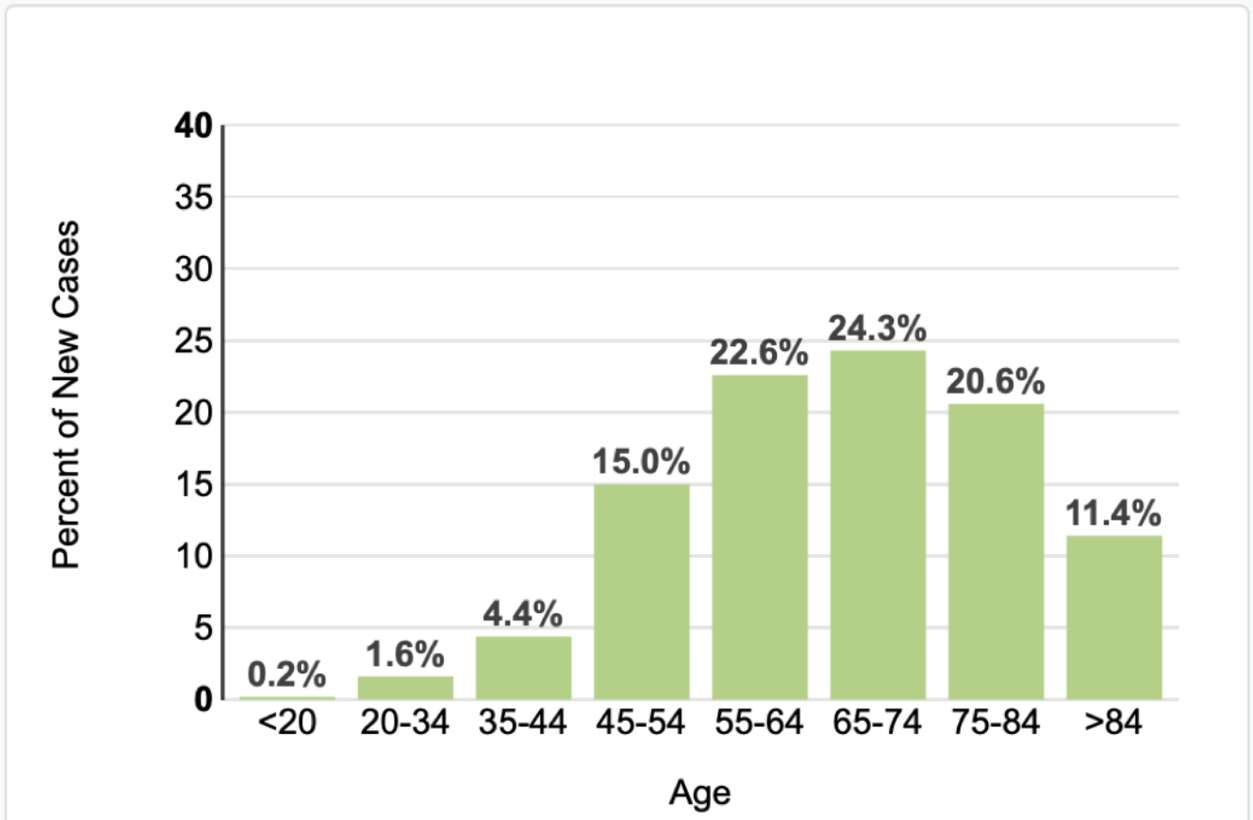
### Cancer Deaths, 2018




- Lung and bronchus: 154,050
- Colon and rectum: 50,630
- Pancreas: 44,330
- Breast: 41,400
- Other: 319,230

seer.cancer.gov - accessed May 2019

## Percent of New Cases by Age Group: Colorectal Cancer




Colorectal cancer is most frequently diagnosed among people aged 65-74.

| Median Age At Diagnosis |
| --- |
| 67 |

SEER 18 2011-2015, All Races, Both Sexes

seer.cancer.gov - accessed May 2019

# Epidemiology

- Lifetime risk of developing CRC is 5%
- Males have a 25% higher risk than females
- African Americans have a 20% higher risk
- Rising incidence of CRC in younger age group <50
- Shift in right sided colon cancer

Uptodate-accessed May 2019

# Risk and Protective Factors

**NON-MODIFIABLE RISK FACTORS**

- Age > 50 yo
- Family history of colorectal cancer
- Personal history of colorectal cancer
- Polyps in the colon and/or rectum
- Inflammatory Bowel Disease (Ulcerative Colitis , Crohn's Disease)
- Lynch Syndrome†
- Familial adenomatous polyposis (FAP)‡

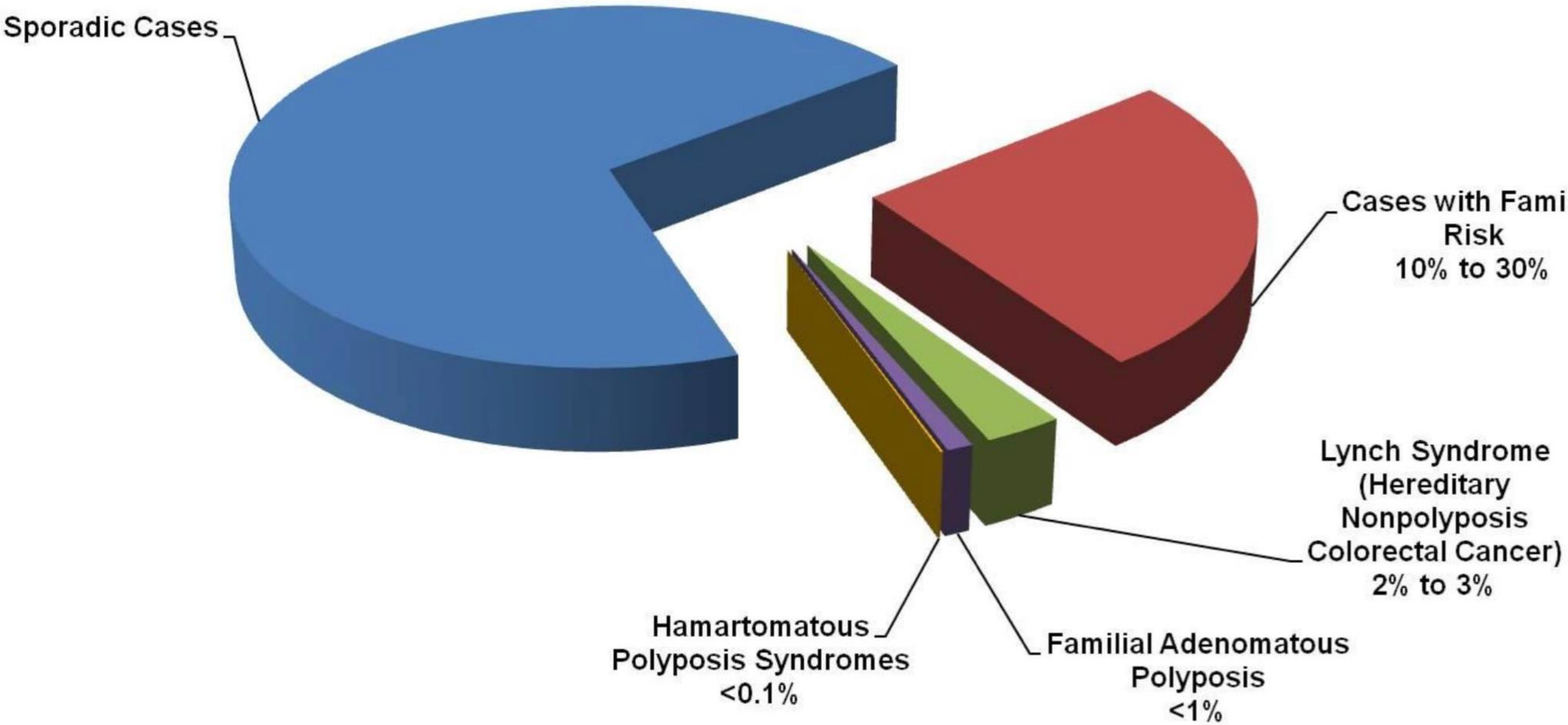
**MODIFIABLE RISK FACTORS**

- Alcohol Consumption
- Smoking Tobacco
- Being overweight or obese
- Not being physically active
- Consuming an abundance of red meats and/or processed meats
- Having a diet low in fibre, fruits and vegetables

| Decreased risk |
| --- |
| Multivitamins containing folic acid |
| Aspirin and other NSAIDs |
| Postmenopausal hormone use |
| Calcium supplementation |
| Selenium |
| Consumption of vegetables, fruits, and fiber |

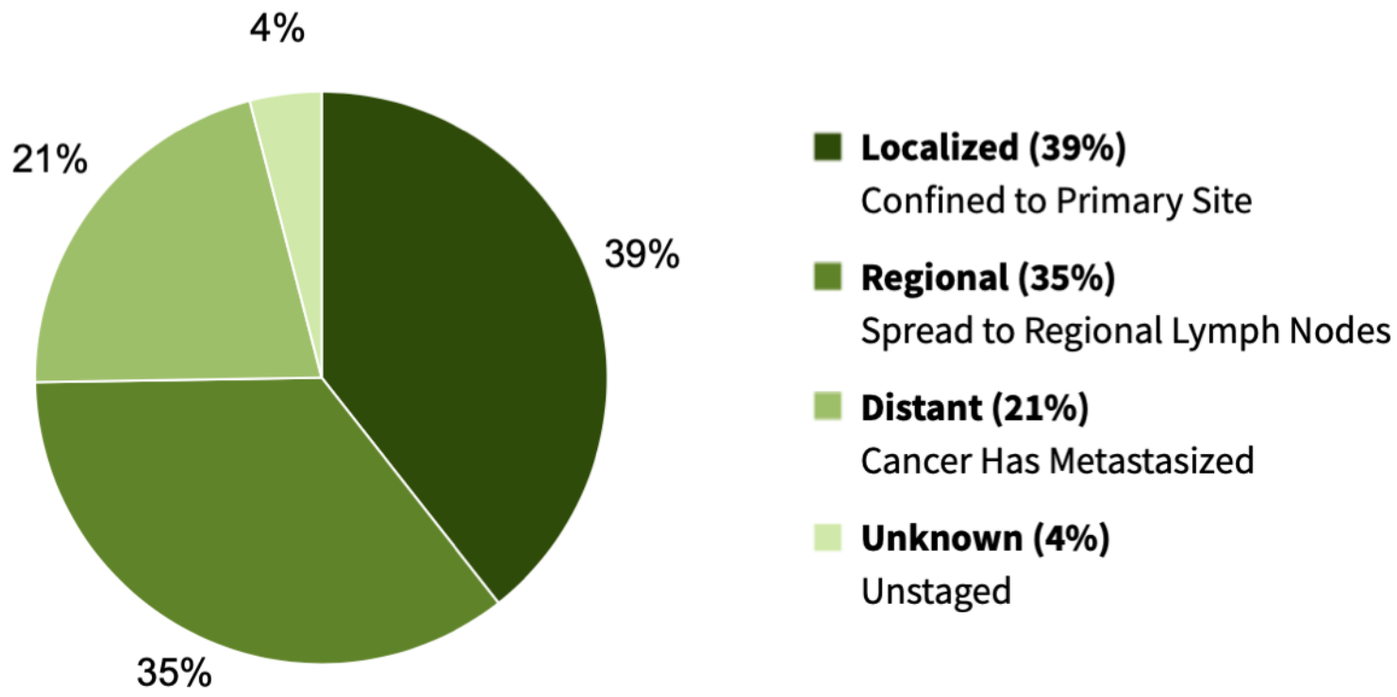
Uptodate-accessed May 2019

# Colon Cancer Cases Arising in Various Family Risk Settings

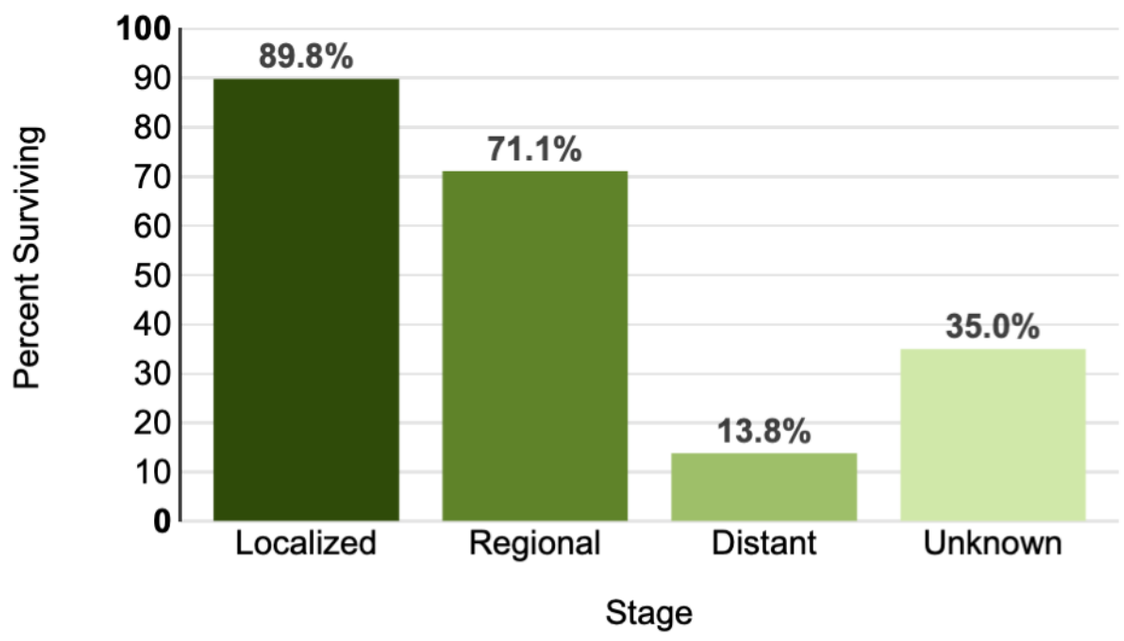



Lynch et al; NEJM 2003;348:919-932

## Percent of Cases by Stage



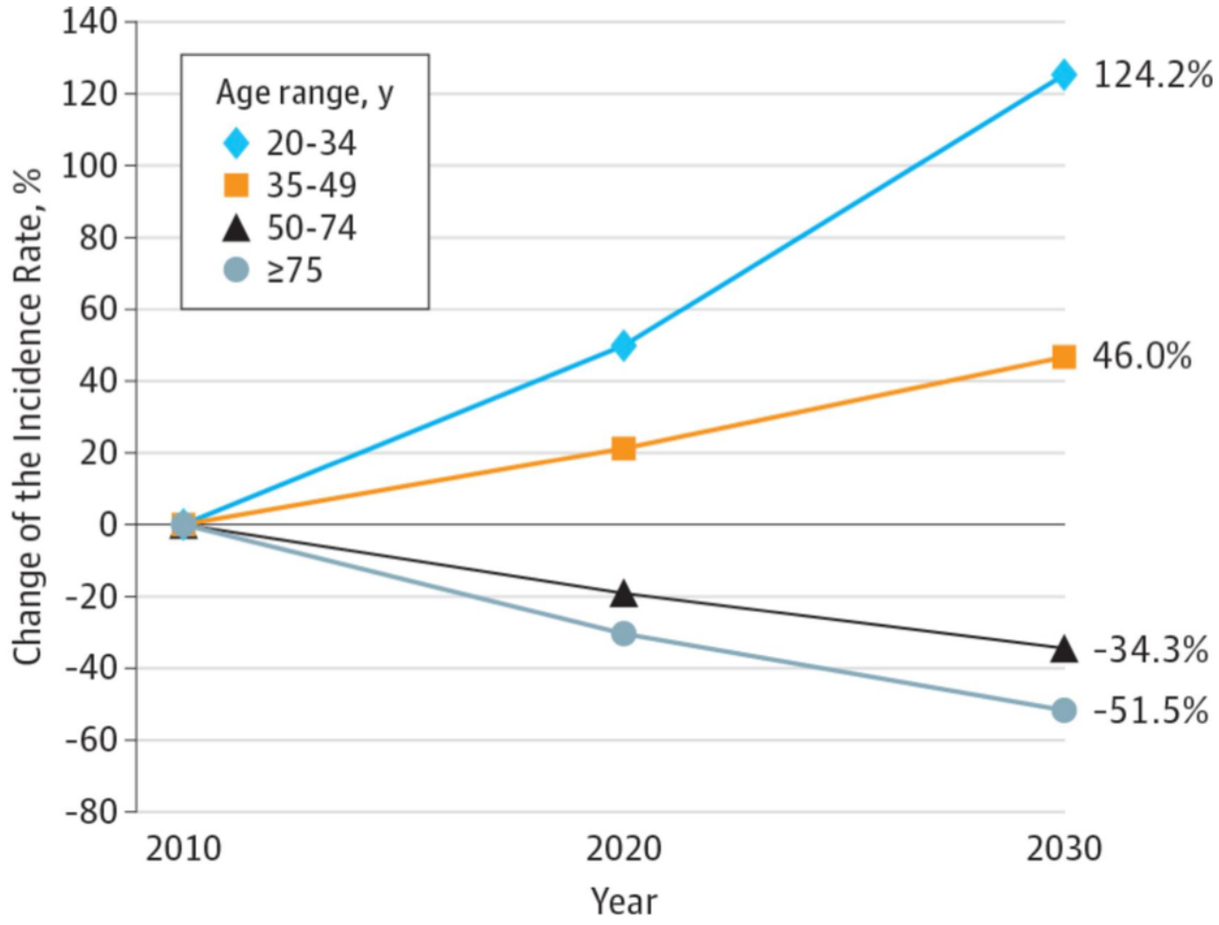

## 5-Year Relative Survival



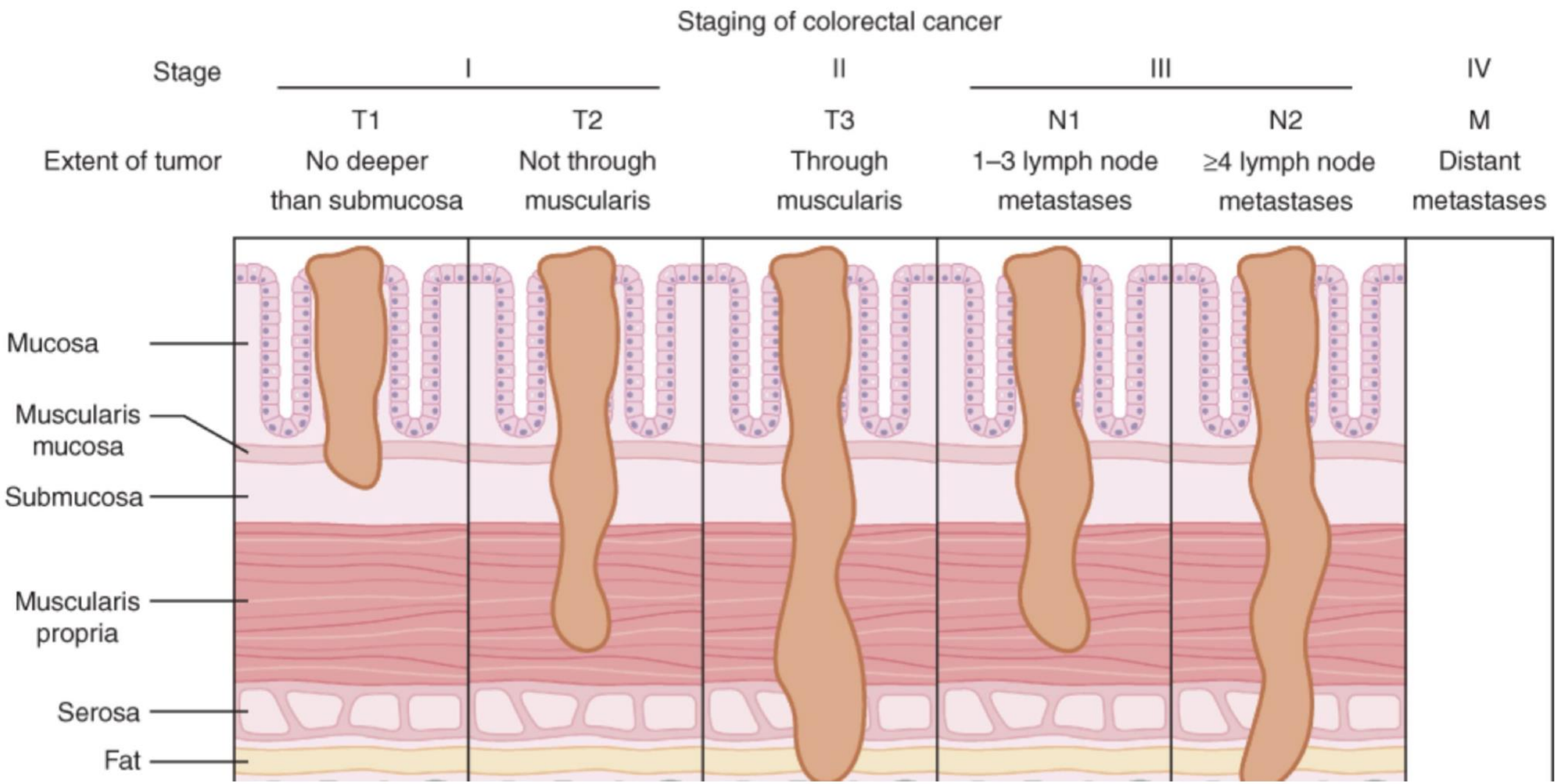

seer.cancer.gov - accessed May 2019

# Rising Incidence of younger age onset CRC

Ages 20-39 - Colon cancer incidence increased by 1-2.4% per annum and rectal cancer by 3.2%
Proportion of rectal cancer cases that were diagnosed in adults younger than age 55 doubled from 14.6% between 1989 and 1990 to 29.2% between 2012 and 2013.



# Staging


Staging of colorectal cancer
Stage
I
II
III
IV
T1
T2
T3
N1
N2
M
Extent of tumor
No deeper than submucosa
Not through muscularis
Through muscularis
1–3 lymph node metastases
≥4 lymph node metastases
Distant metastases
Mucosa
Muscularis mucosa
Submucosa
Muscularis propria
Serosa
Fat

# Screening

**ACS screening options for adults age 45 years and older who are at average risk of colorectal cancer include either a high-sensitivity, stool-based test or a visual exam**

| | Test | Frequency |
|---|---|---|
| **Stool-based** | FIT | Every year |
| | Highly-sensitive-guaiac-based fecal occult blood test (HSgFOBT) | Every year |
| | Multi-targeted stool DNA test (mt SDNA) | Every 3 years |
| **Visual exams of the colon and rectum** | Colonoscopy | Every 10 years |
| | CT colongraphy (CTC) (virtual colonoscopy) | Every 5 years |
| | Flexible sigmoidoscopy (FS) | Every 5 years |

cancer.org-accessed May 2019

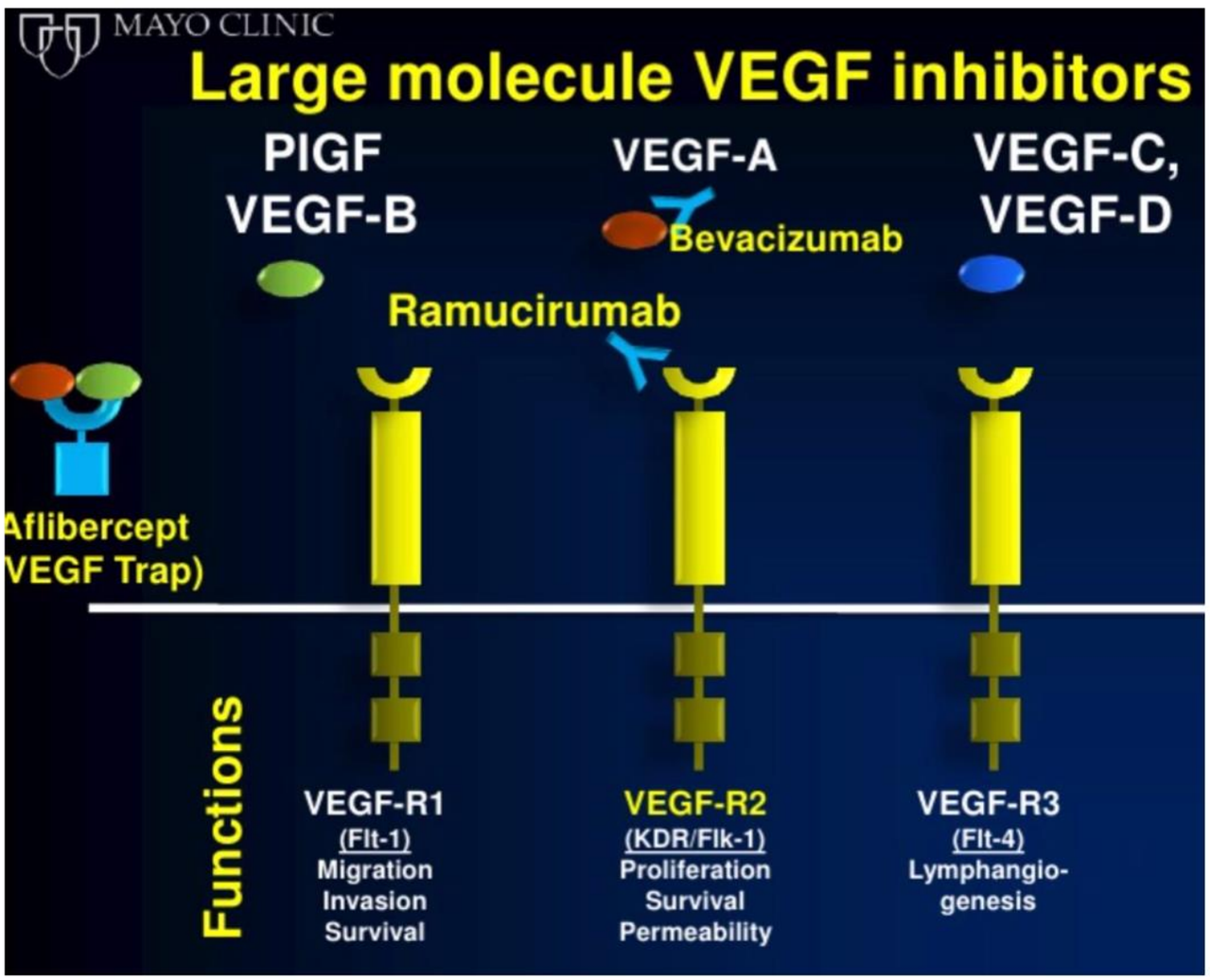
# Treatment

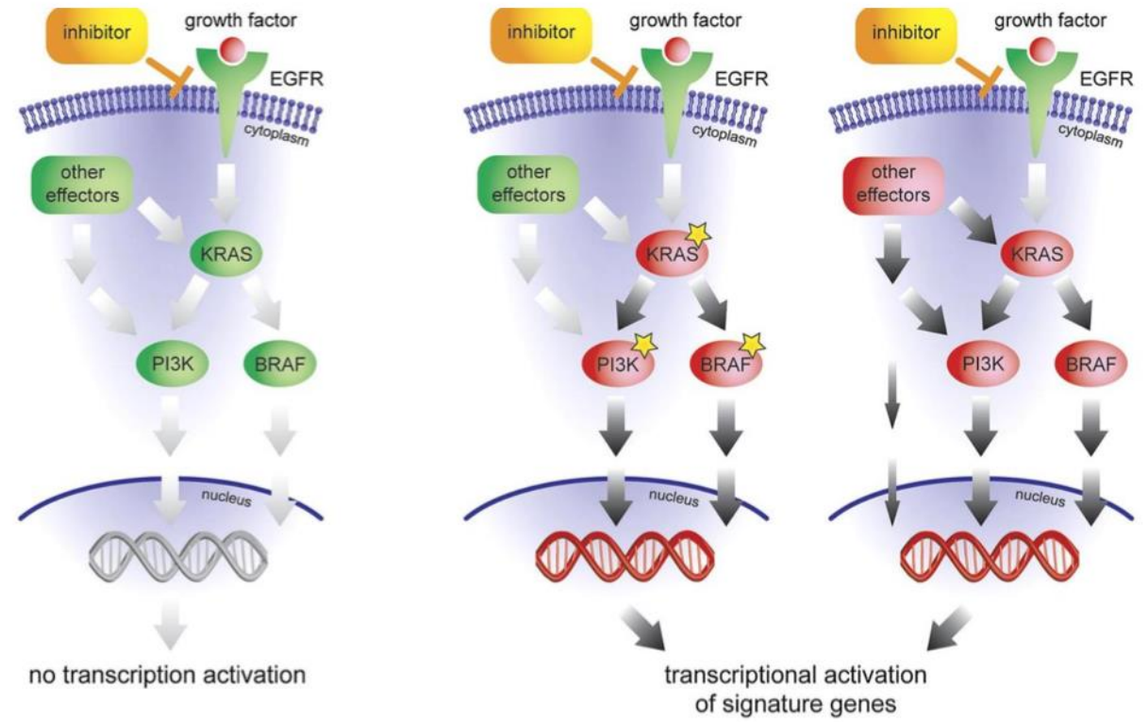
- Stage 1 - surgical resection - No role for adjuvant therapy
- Stage IIA - Benefit of adjuvant chemotherapy modest - ?colon cancer oncotype Dx
- Stage IIB - Recommend chemotherapy
- Stage III - chemotherapy  -3 months for lower risk and 6 months for higher risk
- Stage IV - chemotherapy with/out surgical resection/ablative techniques - subset can be cured
- Rectal cancer - increasing use of total neoadjuvant therapy and possible avoidance of surgery

## 11 FDA Approved Drugs for Colorectal Cancer

| "Cytotoxics" | Mechanism |
|---|---|
| 1. 5-Fluorouracil (5-FU) | -> pyrimidine analog |
| 2. capecitabine | -> oral 5-FU pro-drug |
| 3. TAS-102 | -> 5-FU drug with metabolism inhibitor |
| 4. irinotecan | -> topoisomerase I inhibitor |
| 5. oxaliplatin | -> 3rd generation platinum |

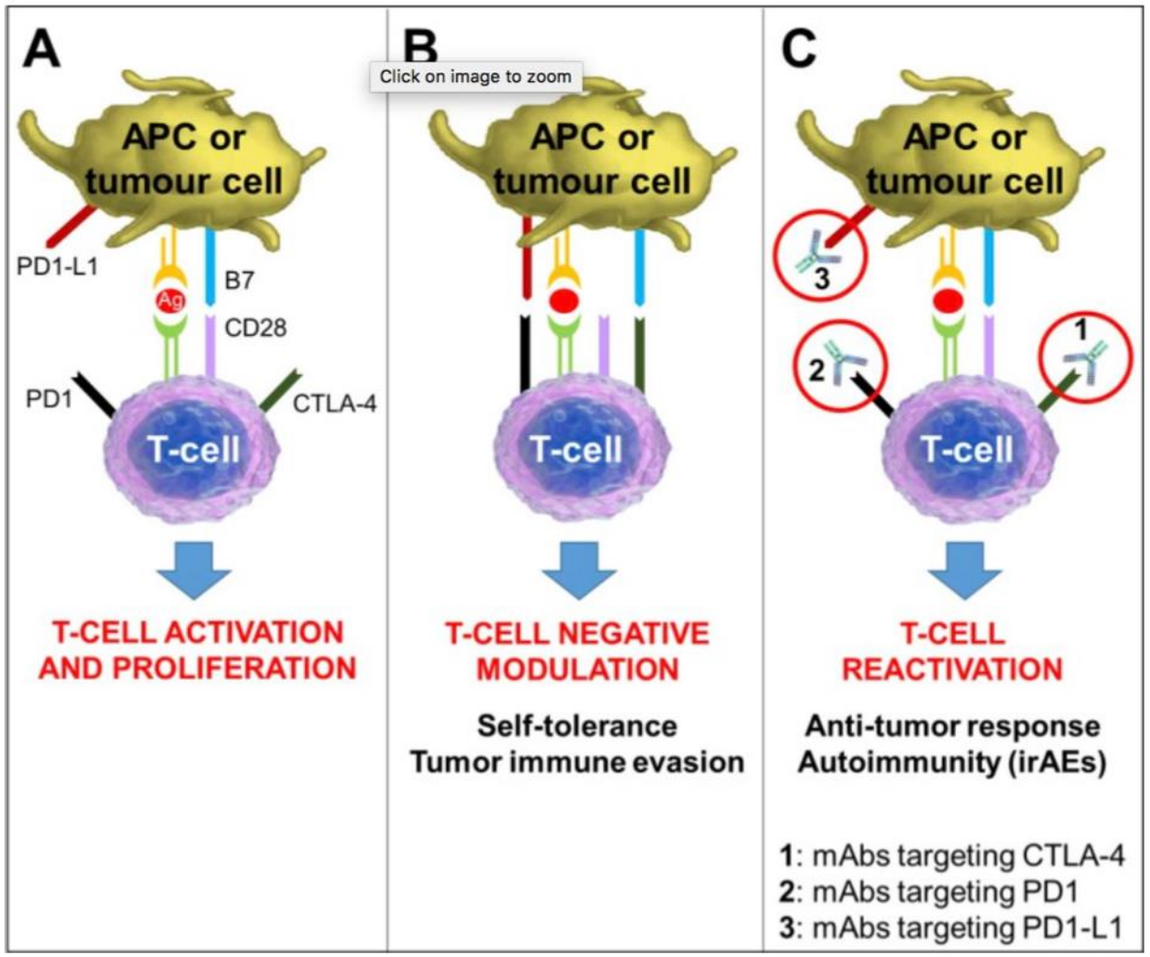
| "Biologics/Targeted" | Mechanism |
|---|---|
| 1. cetuximab | -> antibody against EGFR |
| 2. panitumumab | -> antibody against EGFR |
| 3. bevacizumab | -> antibody against VEGF |
| 4. ziv-aflibercept | -> VEGF trap |
| 5. regorafenib | -> tyrosine kinase inhibitor |
| 6. ramucirumab | -> antibody against VEGFR2 |

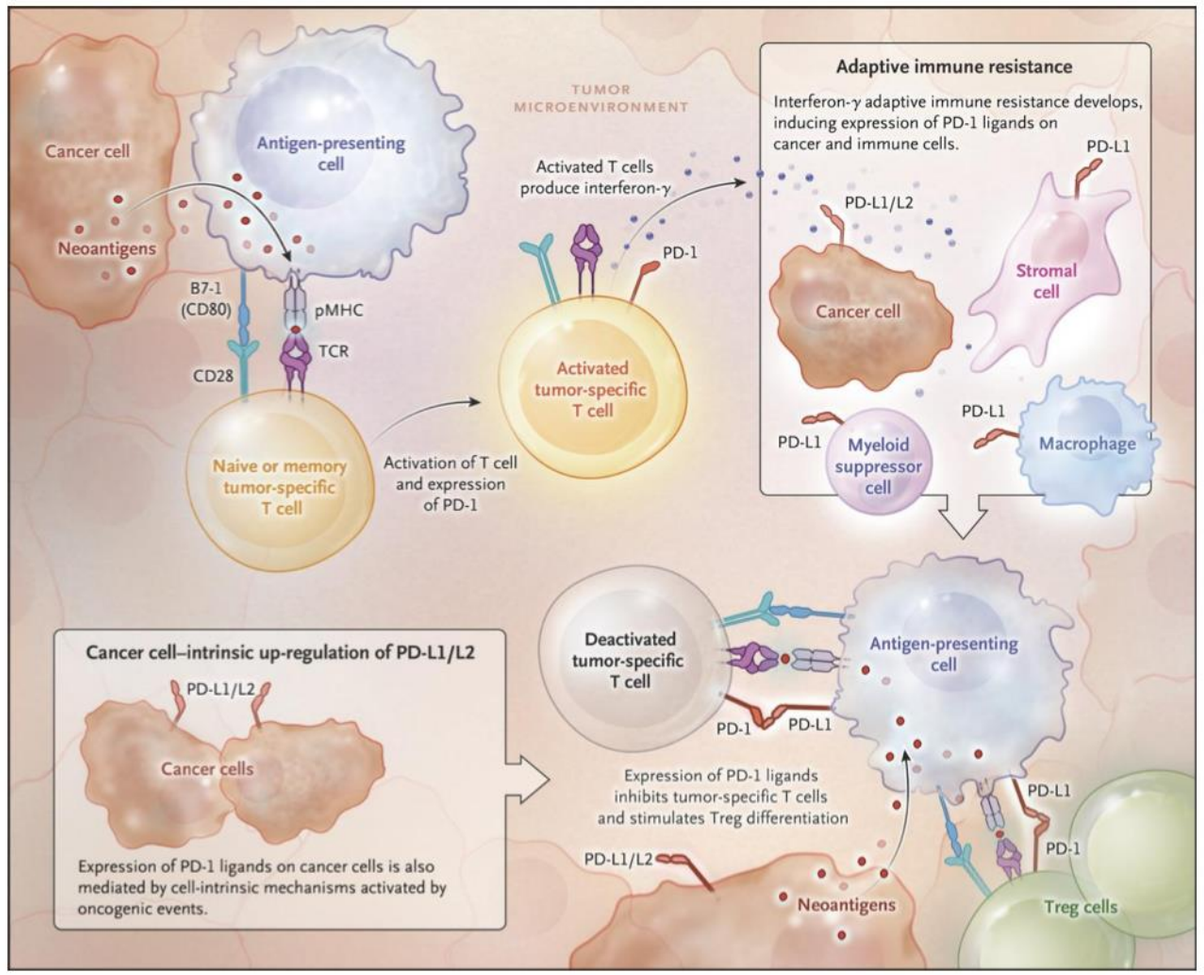



| | |
|---|---|
| Wildtype | Mutant |
| Wildtype-like signature | Activated oncogenic signature |
| Responsive to EGFR inhibition | Resistant to EGFR inhibition |
| | Wildtype |

# Immunotherapy and CRC




- MSI high tumors 3-5% of metastatic CRC
- Increased cell surface epitopes leading to increased immunogenicity
- Treatment with immunotherapy in second or later lines of therapy

# Molecular Subtypes

- BRAF V600E - 7% of CRC- more aggressive  - FDA approved options that target BRAF

- Her2  - about 3% of CRC - numerous agents in clinical trials testing anti Her2 agents

- KRAS - early clinical trials looking at drugs targeting KRAS - preliminary testing in CRC

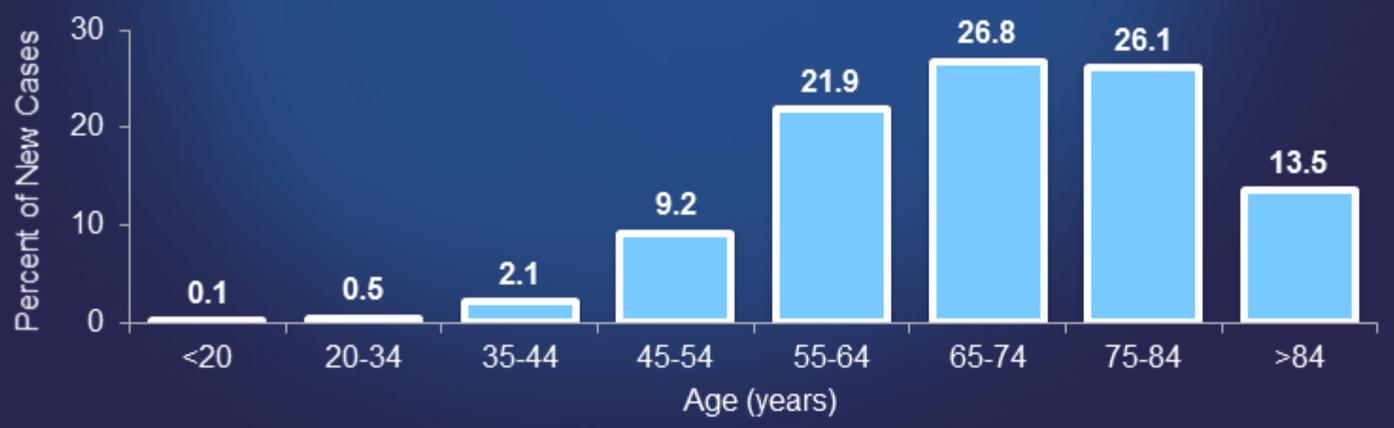
# Pancreatic Cancer Epidemiology

## Estimated Cancer Deaths in 2016[1]

| Men | | | | Women | | |
|---|---|---|---|---|---|---|
| Lung and bronchus | 85,920 | 27% | | 26% | 72,160 | Lung and bronchus |
| Prostate | 26,120 | 8% | | 14% | 40,450 | Breast |
| Colon and rectum | 26,020 | 8% | | 8% | 23,170 | Colon and rectum |
| **Pancreas** | **21,450** | **7%** | | **7%** | **20,330** | **Pancreas** |
| Liver | 18,280 | 6% | | 5% | 14,240 | Ovary |

When genders are combined, pancreatic cancer ranks 3rd among cancer-related causes of death[1]

## Percent of New Cases by Age Group[2,a] (2008-2012)




| Median Age at Diagnosis |
|---|
| 71 |

| % of Patients ≥75 Years |
|---|
| ~40% |

[a] From 18 SEER geographic regions.


1. American Cancer Society. *Cancer Facts & Figures 2016*. Atlanta: American Cancer Society; 2016.
2. National Cancer Institute. SEER Stat Fact Sheets: Pancreas. Accessed January 28, 2016.

# Pancreatic Cancer Risk Factors and Associations

| | Risk | Association |
|---|---|---|
| **Demographic** | • Older age | • Male gender |
| **Genetic or Medical** | • Family history<br>• Chronic pancreatitis<br>• Long standing diabetes mellitus | • Obesity<br>• Non-O blood group |
| **Environment** | • Cigarette smoking | • Occupational exposures<br>• High-fat diet<br>• Diets high in meat and low in vegetables and folate |

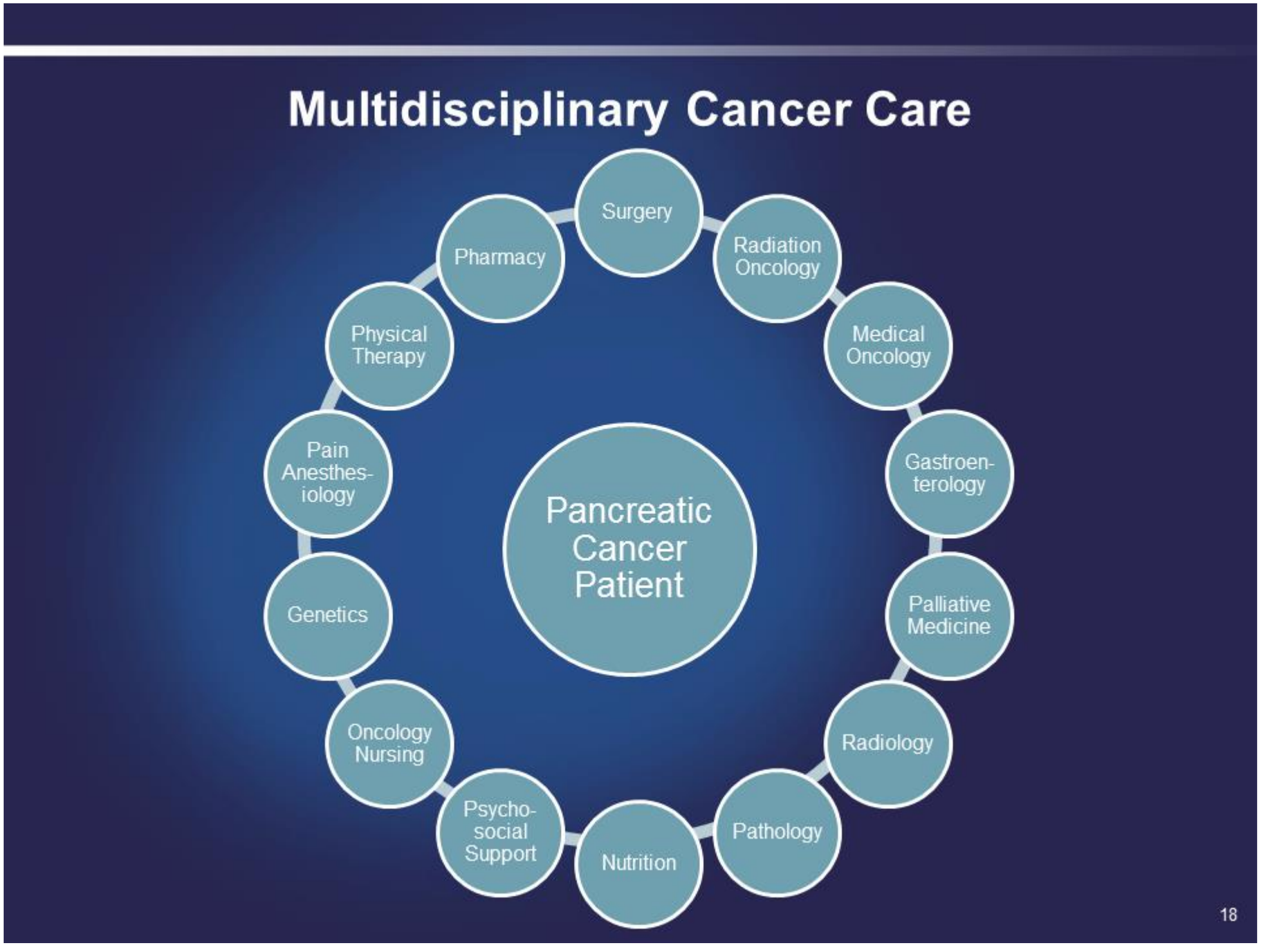
Vincent A, et al. *Lancet*. 2011;378(9791):607-20.

# Genetic Susceptibility to Pancreatic Cancer

- ~7%-10% of affected individuals with pancreatic cancer have a family history[1]

| Genetic Mutations | Type | Syndrome | Risk Level |
|---|---|---|---|
| BRCA1<br>BRCA2 | Germline | Hereditary breast/ovarian cancer syndrome | • BRCA2 mutation is the most common known genetic cause for familial pancreatic cancer[1]<br>• ~3.6%-5% lifetime risk for developing pancreatic cancer[2] |
| PALB2 | Germline | Fanconi anemia type N[3] | • Recorded in up to 3% of patients with familial pancreatic cancer[1]<br>• Lifetime risk for pancreatic cancer is not well defined at this time |
| P16/CDKN2A | Somatic | Familial atypical multiple-mole melanoma | • ~10%-17% lifetime risk for pancreatic cancer[2] |
| STK11/LKB1 | Somatic | Peutz-Jeghers syndrome | • ~11%-36% lifetime risk for pancreatic cancer[2] |
| PRSS1 | Somatic | Hereditary pancreatitis | • ~25%-40% lifetime risk for pancreatic cancer[2] |
| MLH1, MSH2, MSH6, PMS2 | Somatic | Hereditary non-polyposis colon cancer (Lynch syndrome) | • ~3.7% lifetime risk for pancreatic cancer[2] |

1. Vincent A, et al. *Lancet*. 2011;378(9791):607-20.
2. Grover S, Syngal S. *Gastroenterology*. 2010;139(4):1076-80.
3. Tischkowitz M and Xia B. *Cancer Res*. 2010;70:7353-7359.


Multidisciplinary Cancer Care
Surgery
Radiation Oncology
Medical Oncology
Gastroen-terology
Palliative Medicine
Radiology
Pathology
Nutrition
Psycho-social Support
Oncology Nursing
Genetics
Pain Anesthes-iology
Physical Therapy
Pharmacy
Pancreatic Cancer Patient
18

# Systemic Therapy: Biological Challenges of Pancreatic Cancer

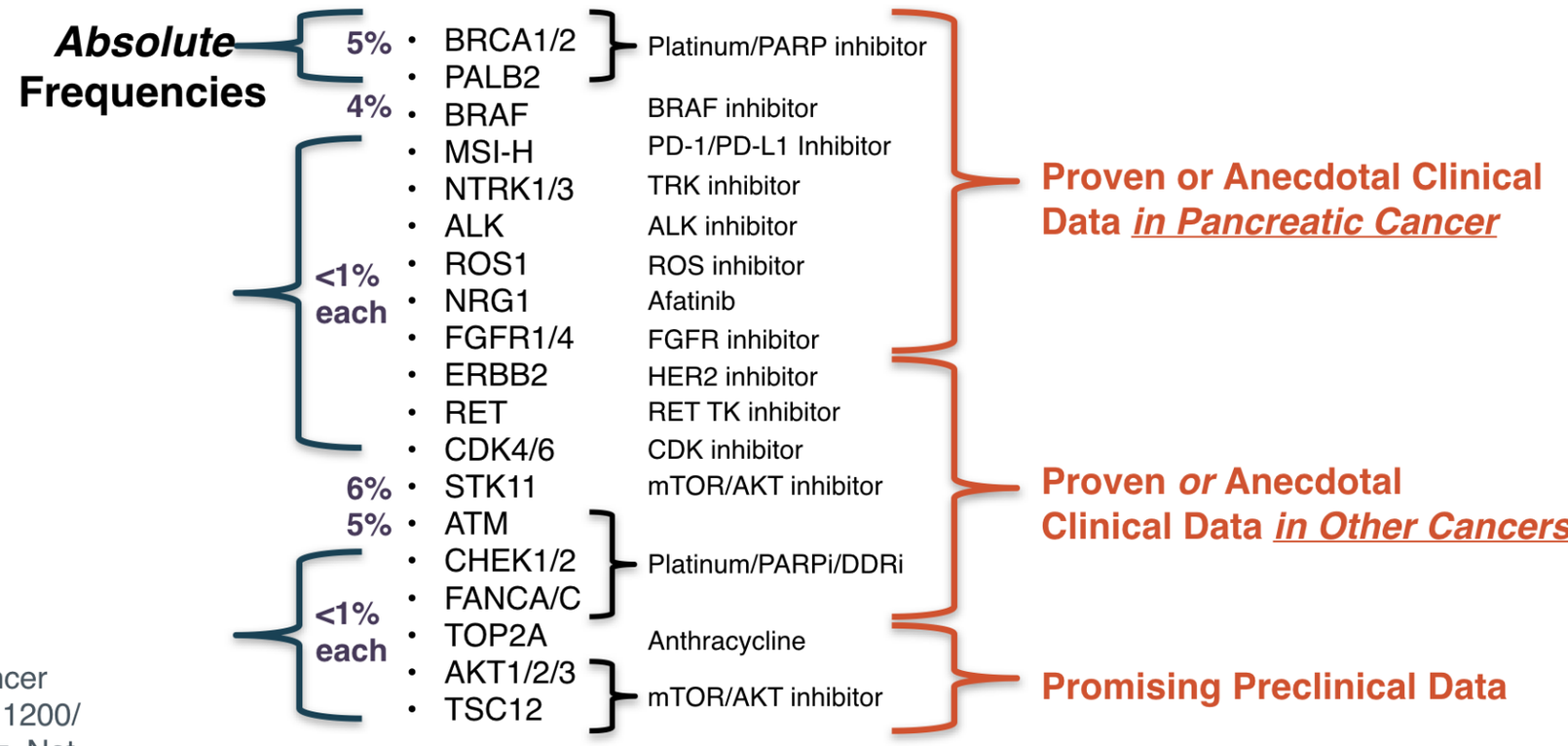
- Stroma as a barrier to drug delivery
- Complex and poorly understood microenvironment
- Immunosuppression
- Multiple gene mutations
- Non-druggable tumor suppressor genes
- Drug resistance
- Lack of biomarkers

# Treatment

- If disease resectable - surgery
- Folfirinox chemotherapy is standard of care following surgical resection
- If high risk disease usually chemotherapy +- radiation followed by possible surgery
- Metastatic disease - folfirinox and gemcitabine/abraxane are standard frontline options
- 5FU + liposomal irinotecan approved for second line if failed prior gemcitabine based regimen
- Multiple trials ongoing looking at different agents usually in combination with chemotherapy

# Pancreatic Cancers DO Harbor Actionable Mutations

- NGS efforts have consistently revealed that ≥ 25% of pancreatic cancers have potentially highly actionable molecular biomarkers




Singhi. Gastroenterology. 2019;156:2242. Pishvaian. Clin Cancer Res. 2018;24:5018. Heeke. JCO Precis Oncol. 2018;2018:10.1200/PO.17.00286. Aguire. Cancer Discov. 2018;8:1096. Witkiewicz. Nat Commun. 2015;6:6744. Lowery. Clin Cancer Res. 2017;23:6094. Waddell. Nature. 2015;518:495. Bailey. Nature. 2016;531:47. Biankin. Nature. 2012;491:399. Collisson. Nat Med. 2011;17:500. Pishvaian. Oncology (Williston Park). 2017;31:168. Jones. Clin Cancer Res. 2019;25:4674.

Slide credit: clinicaloptions.com

# How Do We Identify These DDR Mutations?

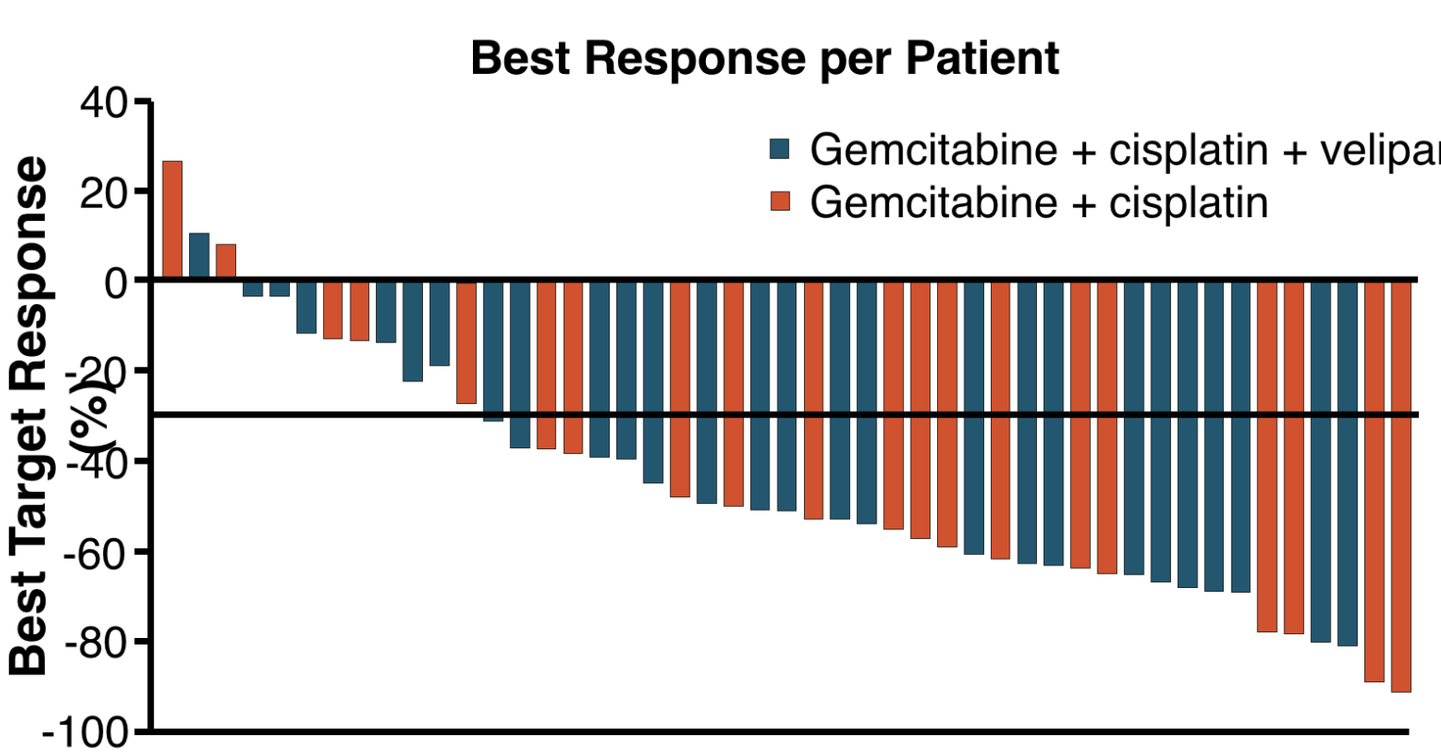
- Germline mutations
  - Mutations the patient was born with
  - Testing done by DNA sequencing of NORMAL cells – normal blood cells; oral epithelium (from saliva)
- Somatic mutations
  - Mutations in the tumor (which might be also ones the patient was born with)
  - Testing done by DNA sequencing of the TUMOR cells

# *BRCA1/2* Mutations in Pancreatic Cancer

- 5% to 7% of patients with pancreatic cancer have germline *BRCA1/2* mutations
  - Ashkenazi Jewish heritage: 5% to 16%
  - Familial pancreatic cancer: 5% to 19%
  - Familial breast/ovarian cancer: 5% to 10%
- **40% of patients who are germline *BRCA1/2* mutation carriers do NOT have a family history of breast/ovarian cancer**

# Gemcitabine + Cisplatin ± Veliparib for Pancreatic Cancer With Germline *BRCA/PALB2* Mutation

- Randomized phase II study in which untreated locally advanced or metastatic PDAC with germline *BRCA/PALB2* mutations received **gemcitabine + cisplatin ± veliparib** (N = 50)




| Outcome | Gem + Cis + Vel (n = 27) | Gem + Cis (n = 23) | *P* Value |
|---|---|---|---|
| RR, % | 74.1 | 65.2 | .55 |
| DCR, % | 100 | 78.3 | .02 |
| Median OS, mos | 15.5 | 16.4 | .6 |
| Median PFS, mos | 10.1 | 9.7 | .73 |

- Grade 3/4 hematologic AEs numerically more common with gemcitabine + cisplatin + veliparib vs gemcitabine + cisplatin (81% vs 73%)

O'Reilly. ASCO GI 2020. Abstr 639. O'Reilly. JCO;[Epub].

Slide credit: clinicaloptions.com

# DDR Mutations in Pancreatic Cancer

- 17% to 25% of pancreatic adenocarcinomas harbor mutations in DDR genes
  - Homologous recombination DNA damage response and repair (HR-DDR) mutations
  - *BRCA1, BRCA2, ATM, PALB2, ATRX, RAD51*, and others

**KYT Dataset (16.5% HR-DDR)**

| Frequency, n (%) | Patients (N = 616) |
|---|---|
| *ATM* | 28 (4.5) |
| *BRCA2* | 18 (2.9) |
| *SMARC4* | 10 (1.6) |
| *BAP1* | 8 (1.3) |
| *BRCA1* | 8 (1.3) |
| *BRIP1* | 6 (1.0) |
| *PALB2* | 5 (0.8) |
| *CHEK2* | 4 (0.6) |
| *FANCA* | 4 (0.6) |
| *FANCC* | 3 (0.5) |
| *RAD50* | 3 (0.5) |
| *STAG2* | 2 (0.3) |
| *BARD1* | 1 (0.2) |
| *CHEK1* | 1 (0.2) |
| *FANCG* | 1 (0.2) |

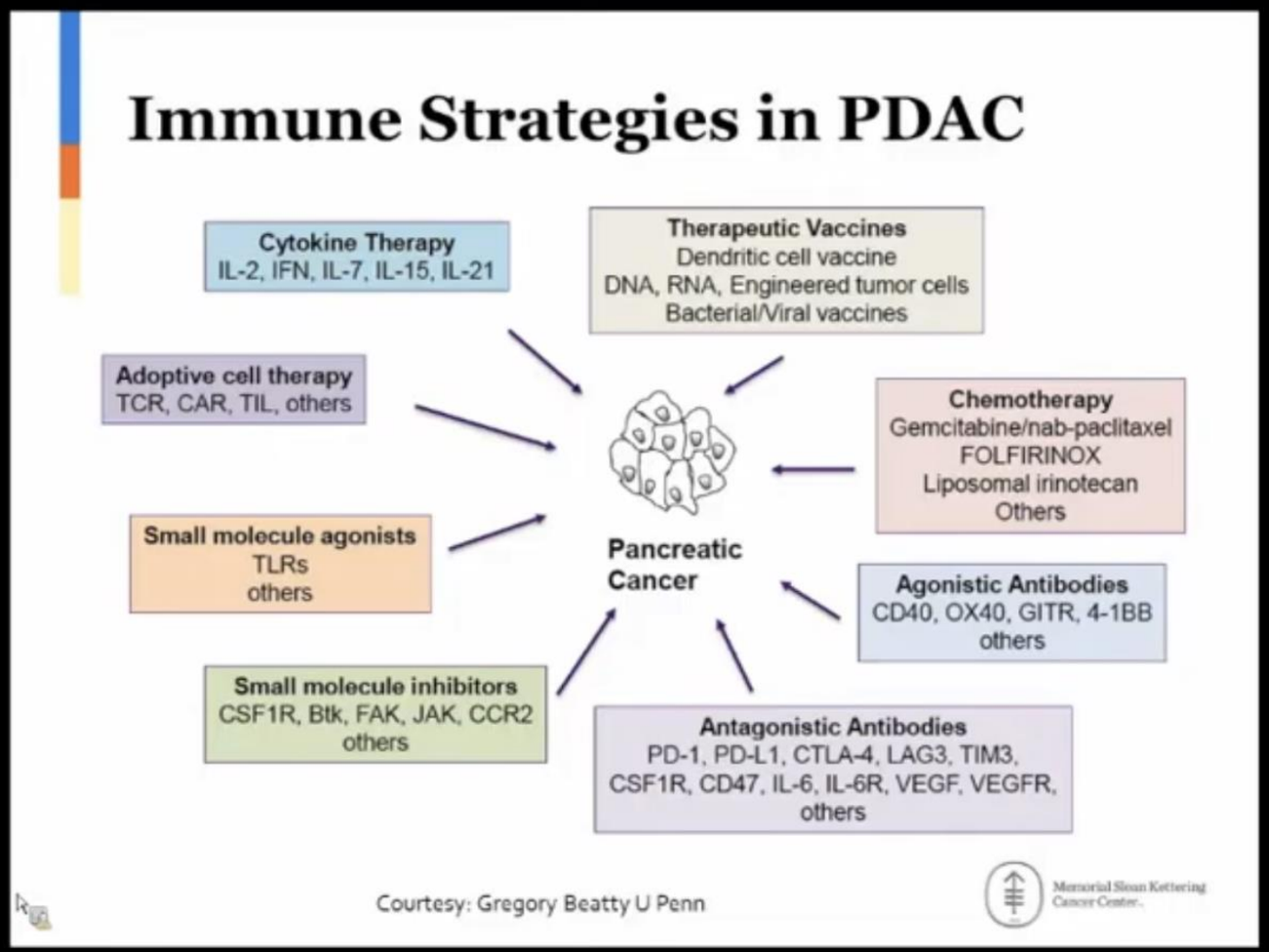
**Caris Dataset (17.4% HR-**

| Pancreas Gene Frequency, % | Patients (N = 833) |
|---|---|
| *ATM* | 3.60 |
| *BRCA2* | 3.33 |
| *BRCA1* | 1.41 |
| *PALB2* | 1.20 |
| *CHEK2* | 0.60 |
| *BAP1* | 0.48 |
| *BRIP1* | 0.48 |
| *NBN* | 0.12 |
| *WRN* | 0.12 |
| *ATRX* | 0 |
| *BLM* | 0 |
| *FANCC* | 0 |
| *MRE11A* | 0 |
| *RAD50* | 0 |
| *ARID1A* | 5.54 |

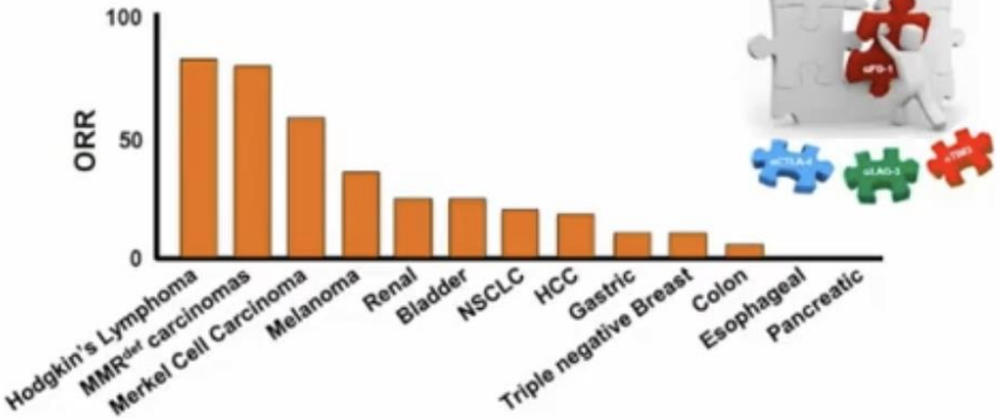
Pishvaian. Clin Cancer Res. 2018;24:5018. Heeke. JCO Precis Oncol. 2018;2018. Aguirre. Cancer Discov. 2018;8:1096. Witkiewicz. Nat Commun. 2015;6:6744. Lowery. Clin Cancer Res. 2017;23:6094. Waddell. Nature. 2015;518:495.
Bailey. Nature. 2016;531:47. Biankin. Nature. 2012;491:399. Collisson. Nat Med. 2011;17:500.

Slide credit: clinicaloptions.com

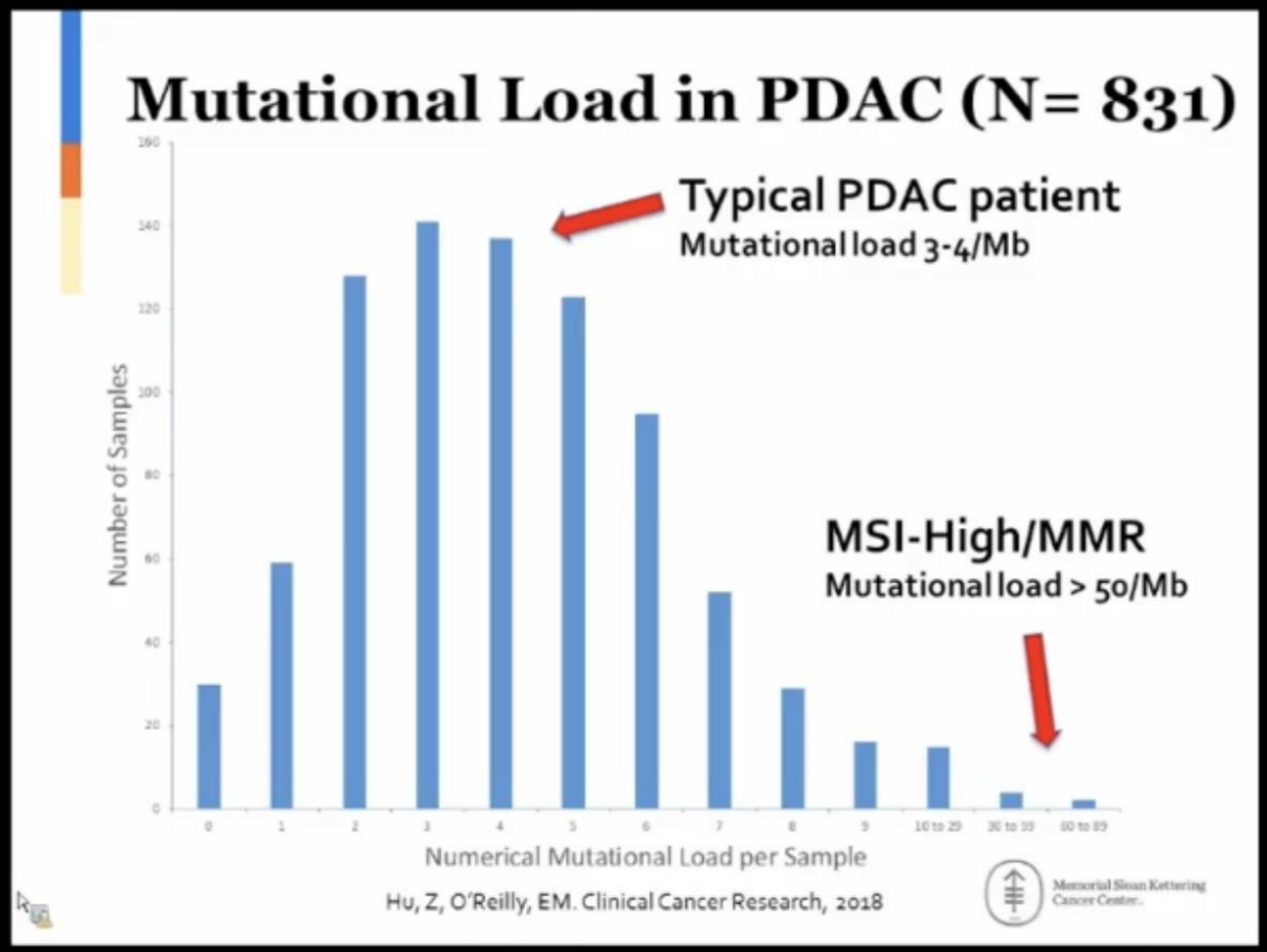
# Immune Strategies in PDAC



# Checkpoint Blockade: Response Rates

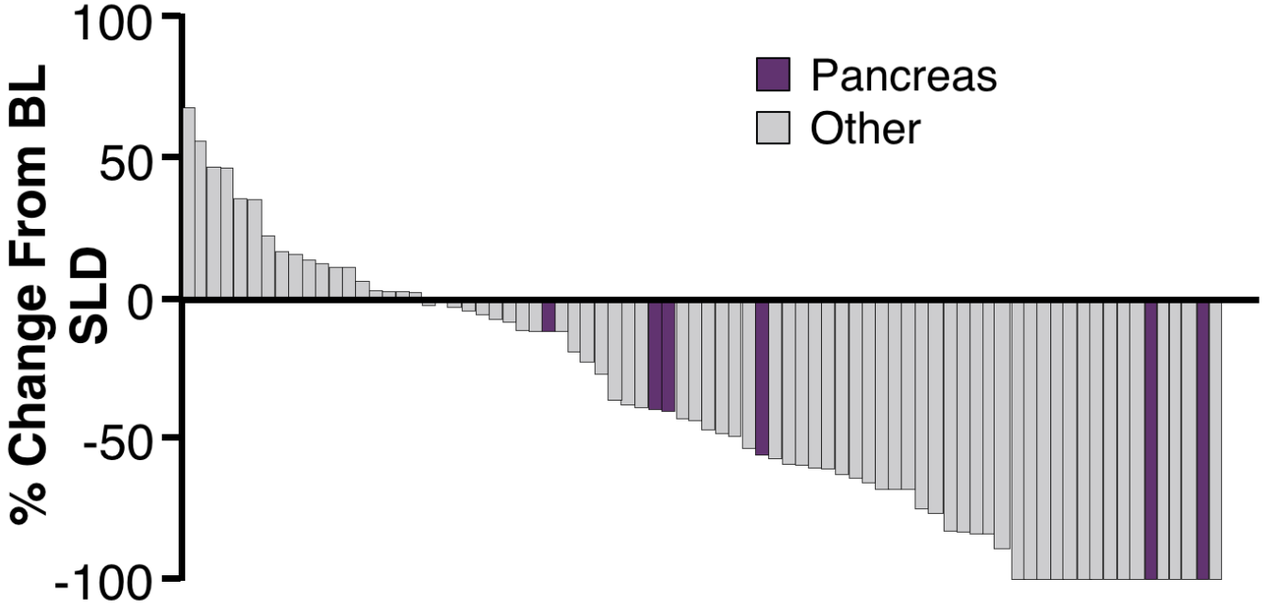


Memorial Sloan Kettering Cancer Center


Mutational Load in PDAC (N= 831)
Typical PDAC patient
Mutational load 3-4/Mb
MSI-High/MMR
Mutational load > 50/Mb
Number of Samples
Numerical Mutational Load per Sample
Hu, Z, O'Reilly, EM. Clinical Cancer Research, 2018
Memorial Sloan Kettering Cancer Center

# MSI-H Pancreatic Cancer

- ~3-5% of CRCs, 22% of gastric cancers, 1% of pancreatic cancers MSI-H
- KEYNOTE-016: 4 of 6 patients with pancreatic cancer responded to pembrolizumab, all benefited[1]



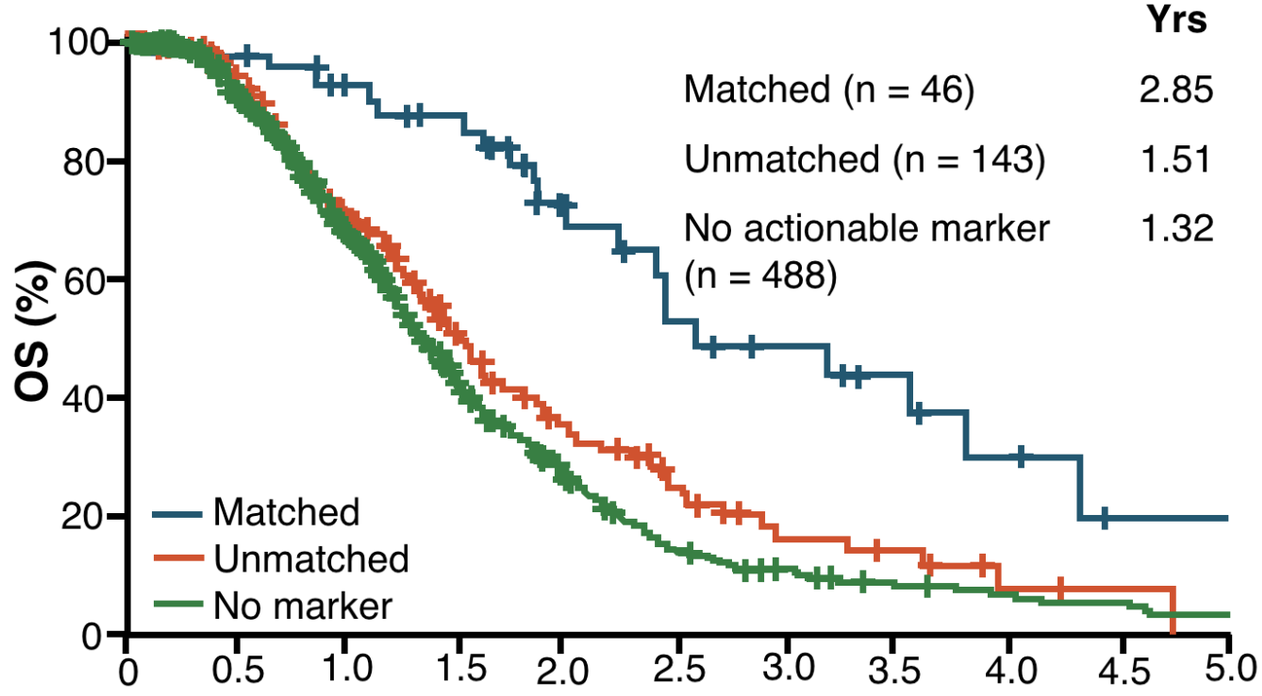

- KEYNOTE-058: ORR only 18.2% in 22 patients; mPFS 2.1 mos and DoR
13.4 mos
  - Lowest compared to all other disease types
  - Need combination therapies to extend the duration of response
- Pembrolizumab approved for patients with high MSI or TMB with PD and no alternative options (tumor agnostic indication)[3]

1. Le. Science. 2017;357:409. 2. Marabelle. J Clin Oncol. 2020;38:1. 3. Pembrolizumab PI.

Slide credit: clinicaloptions.com

# Gold Standard: Overall Survival Benefit

- 1028 pancreatic cancer patients
  - All underwent molecular profiling w/NGS
- 677 patients with outcome information
  - 189 with actionable findings
    - 46 received molecularly matched therapy
    - 143 received “unmatched” therapy
  - 488 with no actionable findings
- Overall survival
  - **Matched 1 y > unmatched**
  - **Matched 1.3 y > no actionable marker**




| Group | mOS, Yrs |
|---|---|
| Matched (n = 46) | 2.85 |
| Unmatched (n = 143) | 1.51 |
| No actionable marker (n = 488) | 1.32 |

| Comparison | HR (95% CI) |
|---|---|
| Matched vs unmatched (highly actionable) | 0.42 (0.26-0.68); *P* = .0004 |
| Matched vs no actionable marker | 0.34 (0.22-0.53); *P* < .0001 |

Pishvaian. Lancet Oncol. 2020;21:508.

Slide credit: clinicaloptions.com