Impact of genomic tests on breast cancer therapy

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Topics to discuss

- Types of genomic tests
- Current uses
  - Is my breast cancer familial/inherited?
  - Could a PARP inhibitor help me?
  - Do I need chemotherapy?
  - Should I have immunotherapy?
  - Am I eligible for a clinical trial?
- Future
  - Individualized therapy
  - Monitoring
  - Population testing?

Genomic testing

Germline

- **Inherited**
- Present in all cells
  - Usually done on blood or cheek cells
  - May be identified in genomic tests done on the tumor
- Risk varies
- Few currently impact treatment of active disease

Somatic

- **NOT inherited**
- Present only in tumor
  - May only be present in a subset of tumor cells
  - May be tested in blood
- No Impact on risk for family
- May guide treatment of active disease

Is my breast cancer inherited?

Regardless of family hx

- Age ≤ 45
- TNBC ≤ age 60
- Two breast cancers: 1st ≤ age 50
- Male
- Ashkenazi Jewish heritage
- Personal hx of ovarian cancer
- Known mutation in the family
- Tumor somatic testing identified BRCA mutation

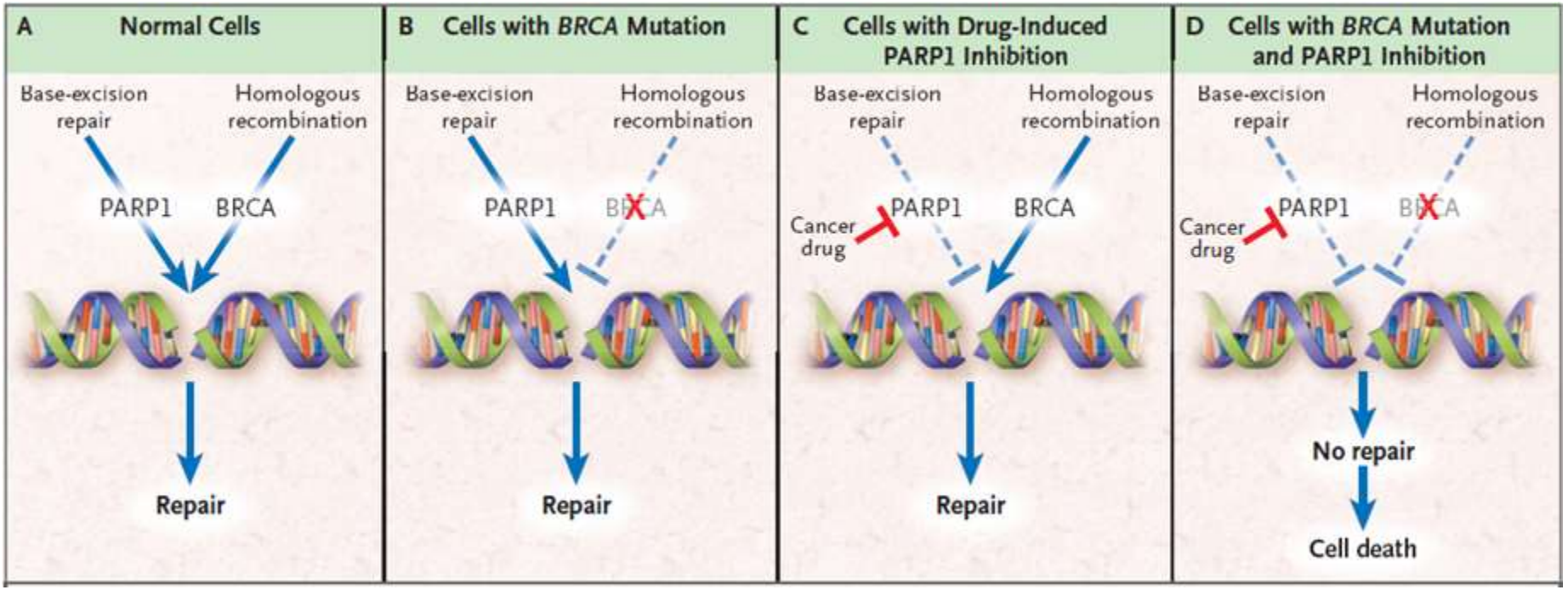
Family history

- Age 46-50:
  - ≥ 1 relative (any age):
    - Breast, Pancreatic, Prostate
    - Limited family hx
- Any age (> 50)
  - ≥ 1 relative:
    - Breast ≤ 50, Ovary or Male Breast
  - ≥ 2 relatives (any age):
    - Breast, Pancreatic, Prostate

Why be tested

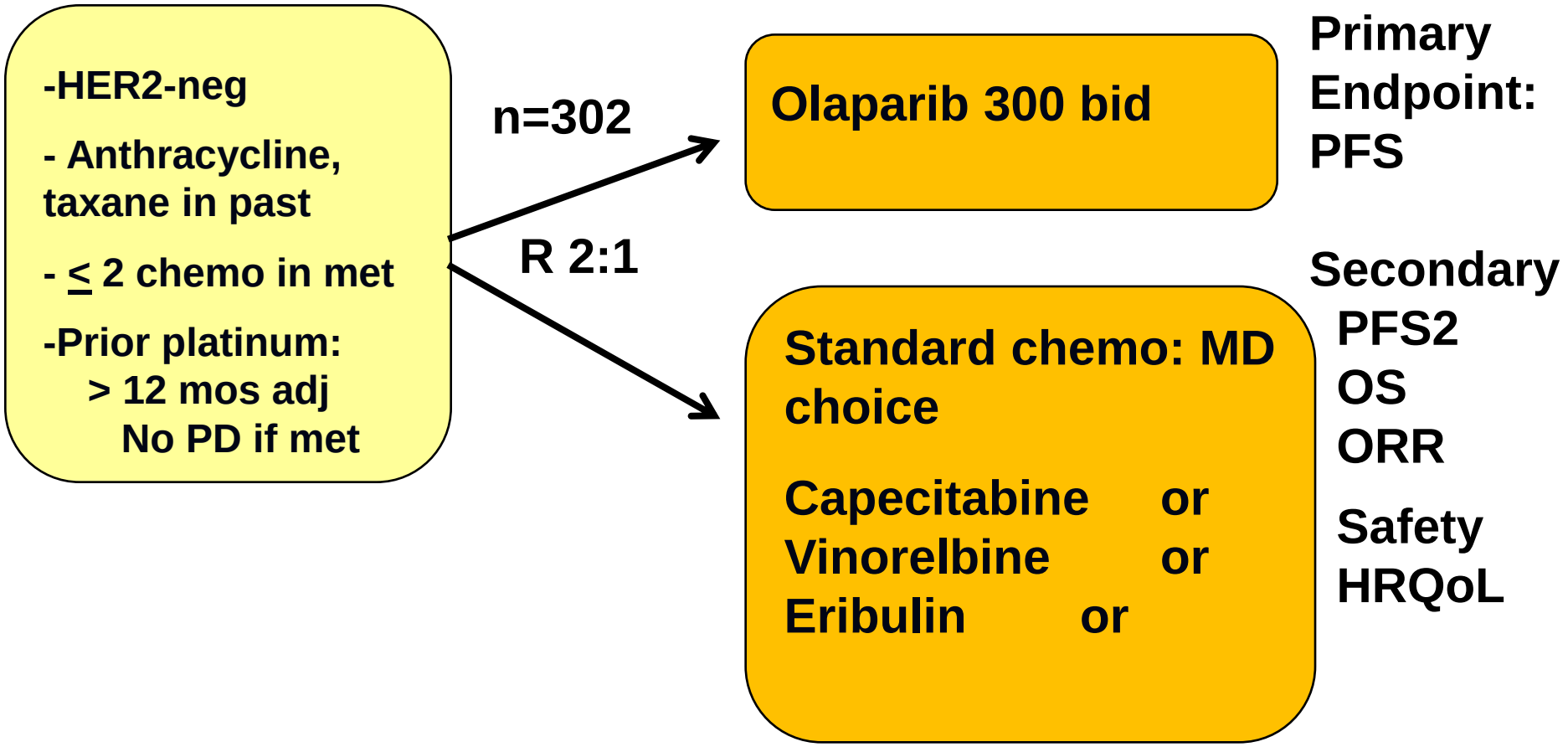
- For your family
  - Determine and manage risk
- For you
  - Change treatment

Could a PARP inhibitor help me?



Iglehart; NEJM 2009

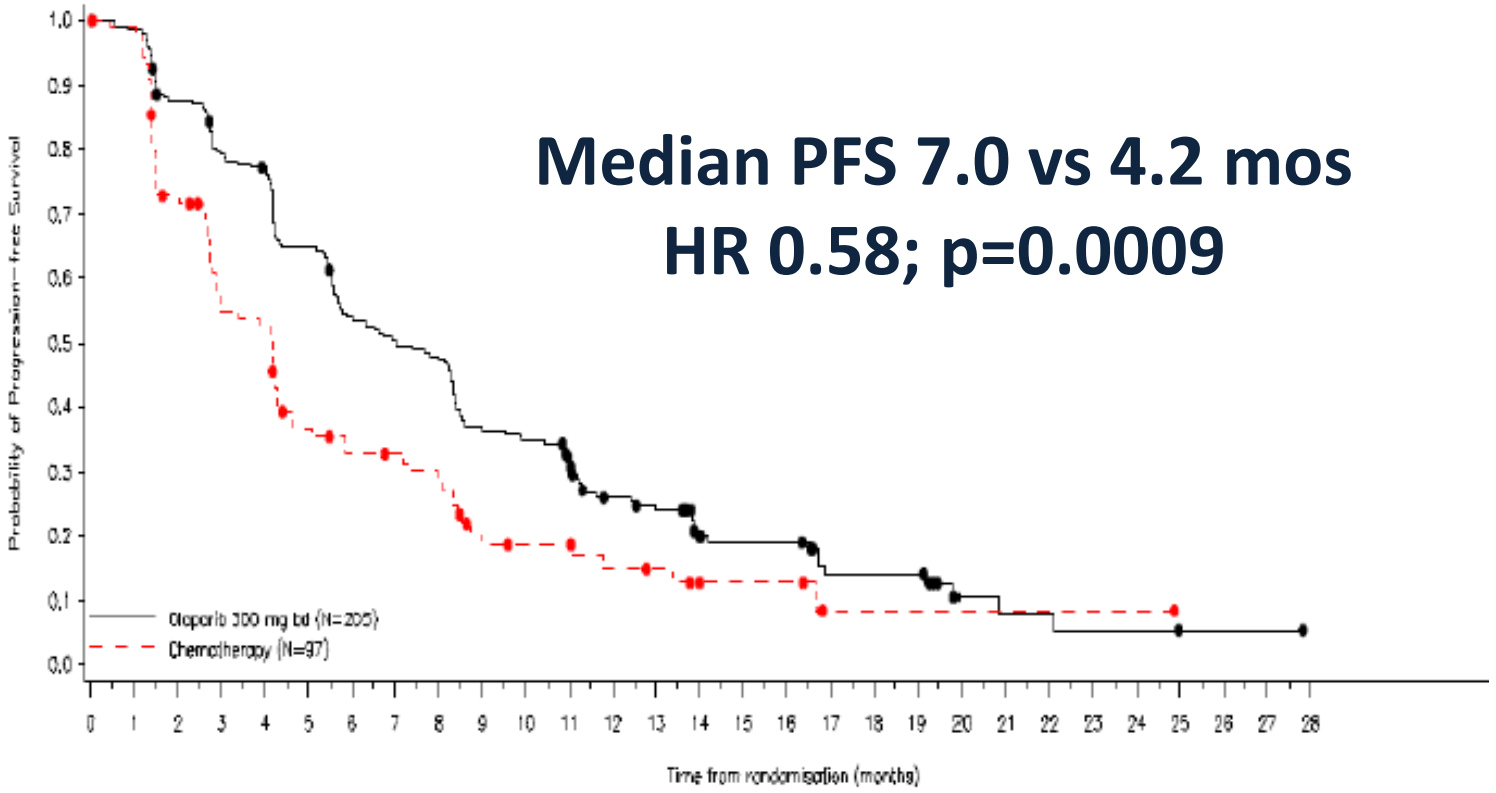
OlympiAD



Robson et al. NEJM; epub June 4, 2017

OlympiAD: olaparib in BRCA+MBC Improved PFS vs chemo

Primary Endpoint: PFS



Median PFS 7.0 vs 4.2 mos
HR 0.58; p=0.0009

Robson et al. NEJM; epub June 4, 2017

Similar results with Talazoparib

	Olaparib	Talazoparib
PFS	7 vs 4.2 (Δ 3 mos) (HR 0.58); p= 0.0009	8.3 vs 5.6 mos (Δ 3 mos) (HR 0.54); p< 0.0001
OS	HR 0.90 (NS)	HR 0.76 (NS)
ORR	59.9%	62.6%
TTR	47 days	-----
QOL	Signif ↑ vs chemo	Signif ↑ vs chemo

PARPi ongoing research

- Patients without BRCA mutations
- Combinations
- Adjuvant therapy

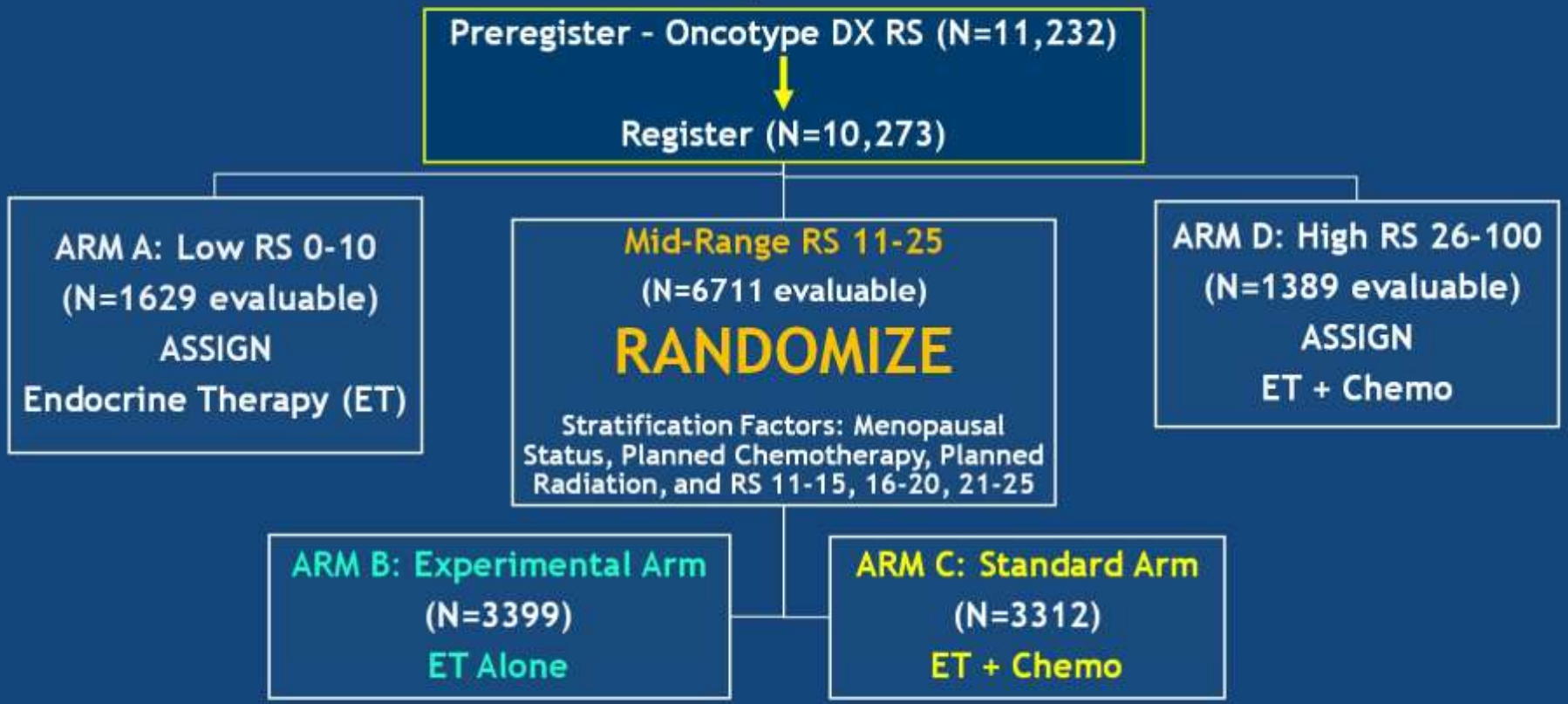
Do I need chemotherapy?

- Chemotherapy increases survival in patients with stage I-III ER+ disease
  - Benefits are small
  - Toxicity is not

- Can we figure out who really needs chemo?

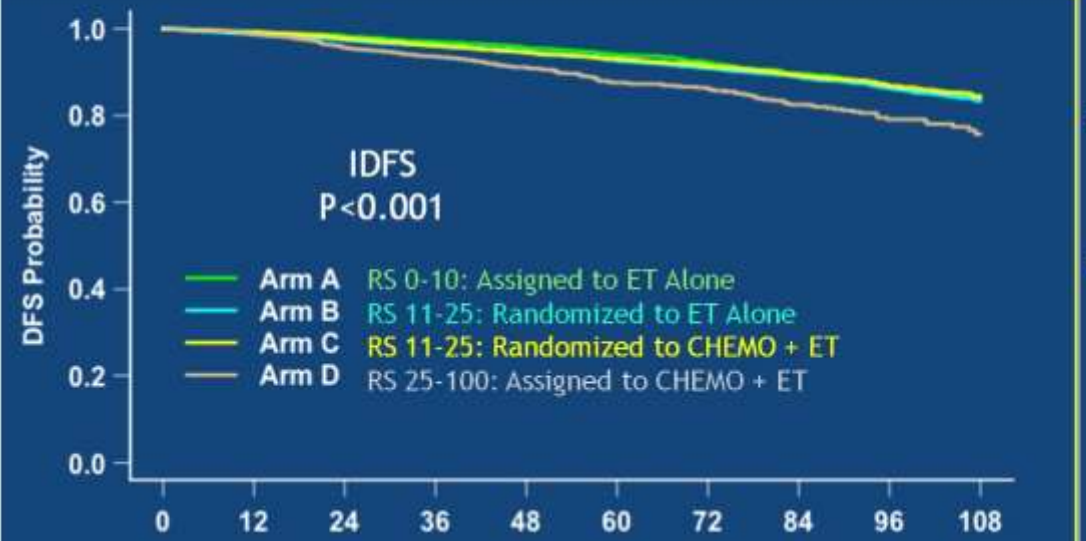
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010



Presented By Joseph Sparano at 2018 ASCO Annual Meeting

TAILORx Results - ITT Population: All Arms (A,B,C & D)



9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone
- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)
- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET

Spares chemotherapy in ~70%

Presented By Joseph Sparano at 2018 ASCO Annual Meeting

Do I need chemo?

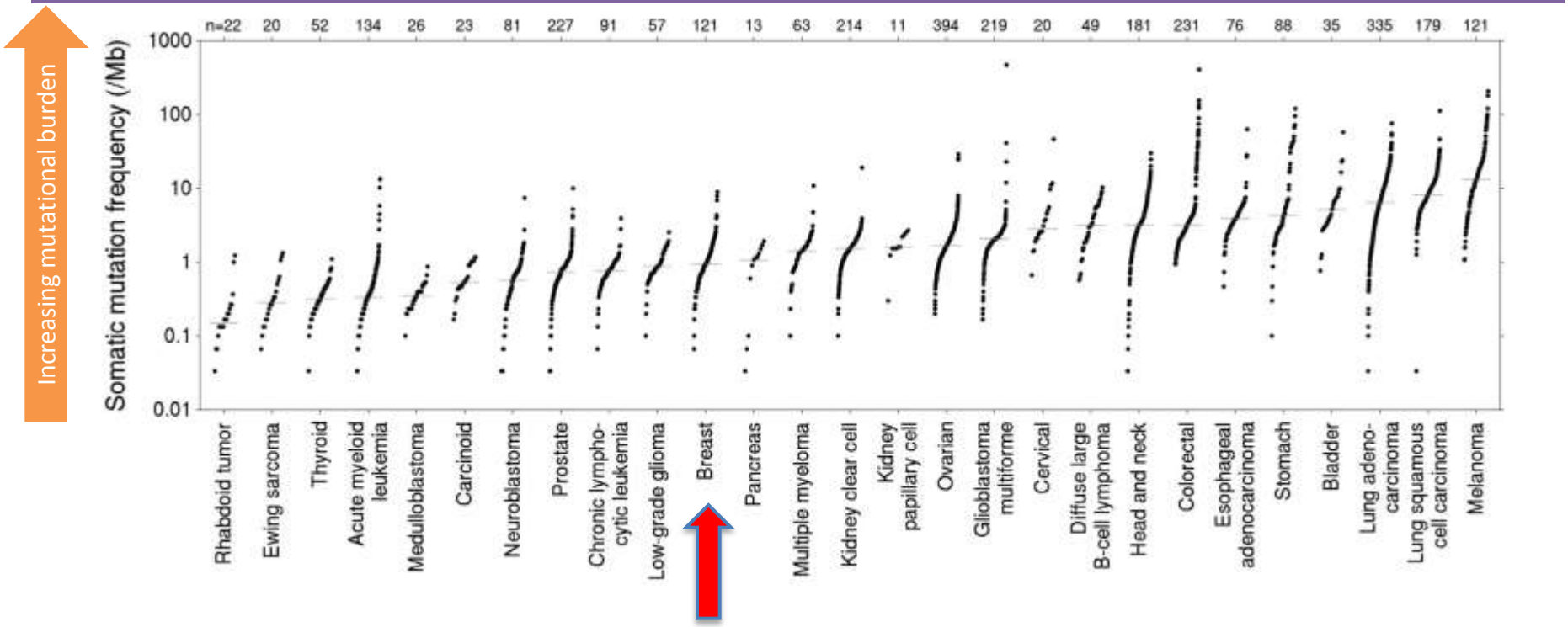
- Oncotype
- Mammaprint
- PAM50
- IHC4
- Endopredict
- Breast Cancer Index (extended hormone Rx?)

Should I have immunotherapy?

- Your immune system isn't faulty
- Cancer came from you
  - Immune system isn't supposed to attack you
- Cancer hijacks normal immune control
  - We've figured out how

Tumor Mutational Burden

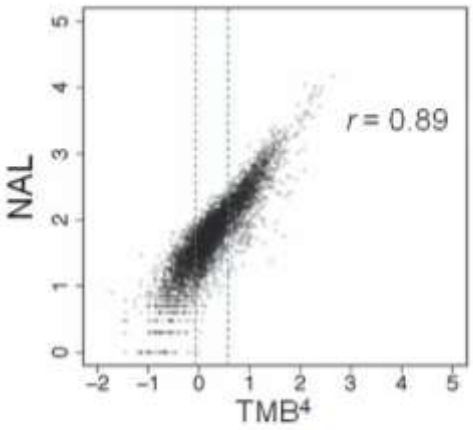
Identification of mutational burden in 27 tumor types using whole genome sequencing[4]

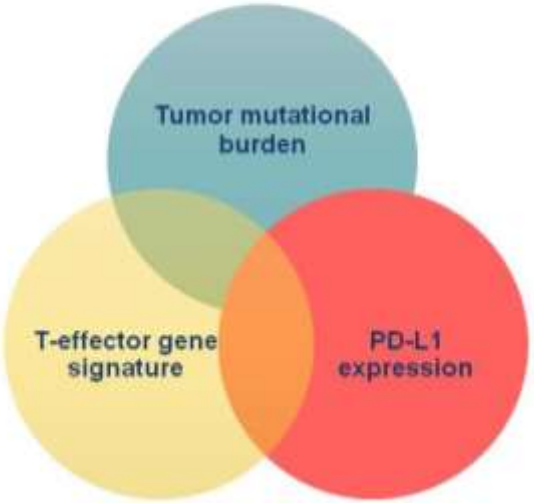


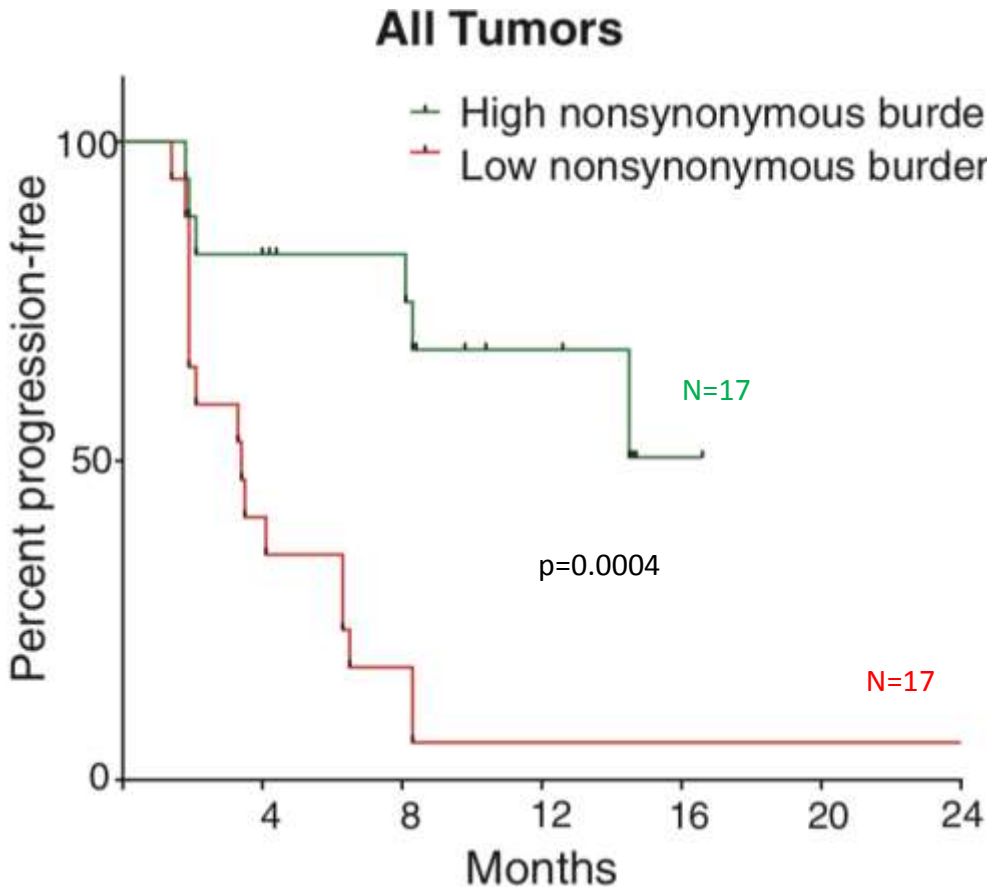
Tumor mutation burden (TMB)

-NS somatic mutations can produce neo-antigens & induce immune response

-Elevated TMB is distinct population from PD-L1+ & MSI-H







KEYNOTE-086: Phase 2 Study of Pembrolizumab Monotherapy For mTNBC

Cohort A
- ≥1 prior systemic treatment for mTNBC with documented PD
- PD-L1 positive or negative

Cohort B
- No prior systemic treatment for mTNBC
- PD-L1 positive

All Patients
- Centrally confirmed TNBC[a]
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample
- No radiographic evidence of CNS metastases

Cohort A N = 170

Cohort B N = 84

Pembrolizumab 200 mg IV Q3W

for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

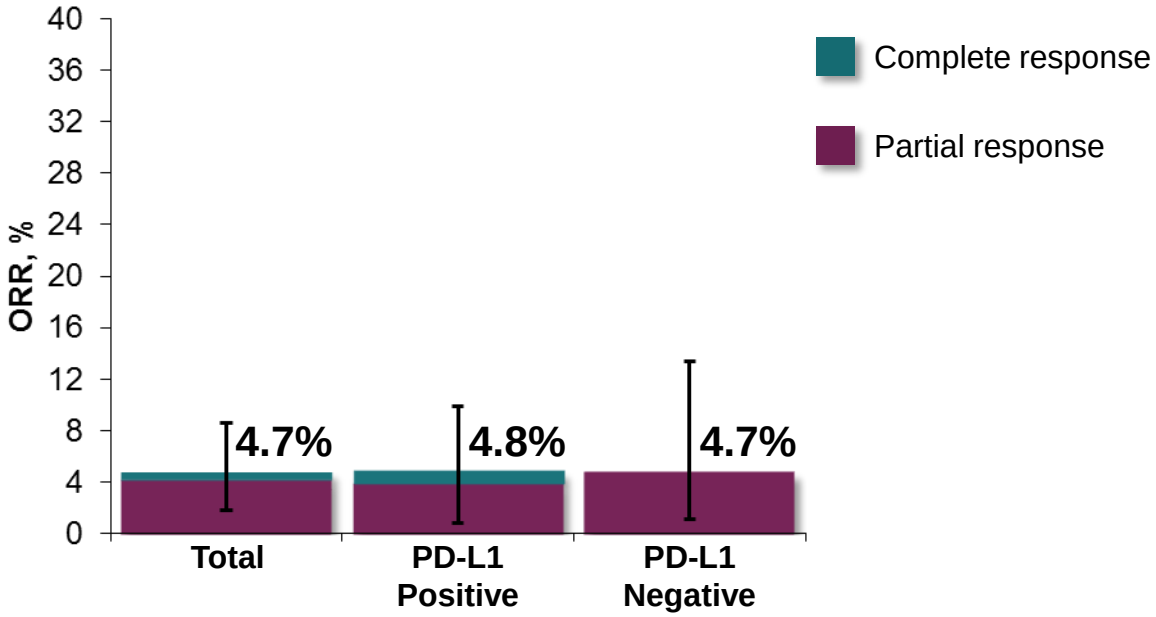
Protocol-specified follow-up

- Primary end points: ORR and safety
- Secondary end points: DOR, DCR,[b] PFS, OS

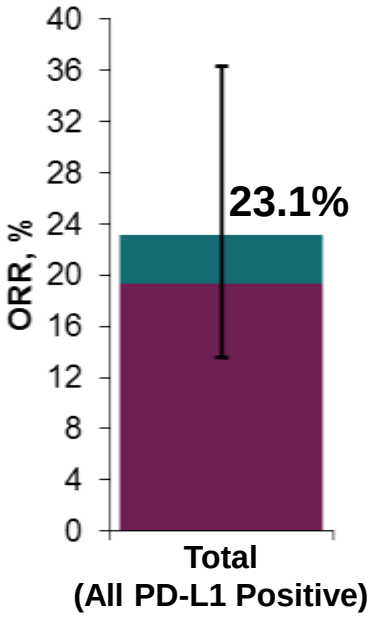
Adams et al. ASCO 2017; Loi et al. ESMO 2017

KEYNOTE-086: Antitumor Activity

Cohort A (N = 170)[1]: Previously Treated mTNBC, Regardless of PD-L1 Expression



Cohort B (N = 52)[2]: Previously Untreated mTNBC, PD-L1 Positive



1. Adams S et al. Presented at ASCO 2017; Jun 2-6, 2017; Chicago, IL, USA; abstr 1008.
2. Adams S et al. Presented at ASCO 2017; Jun 2-6, 2017; Chicago, IL, USA; abstr 1088.

Don’t despair

Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

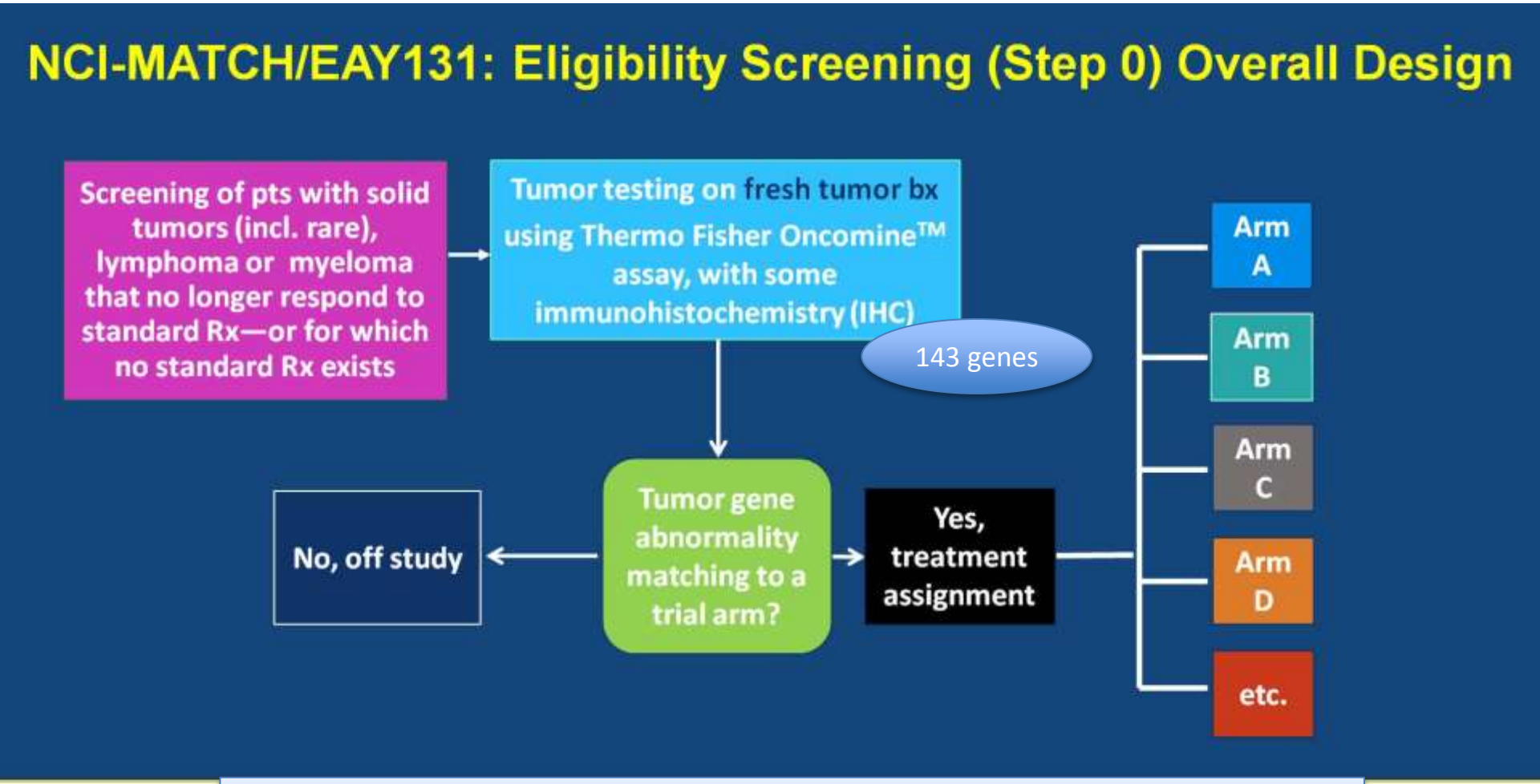
Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	**0.46** (0.34 – 0.58)	**0.16** (0.06 – 0.27)	**> 99%**	**99%**
TNBC	**0.60** (0.43 – 0.78)	**0.20** (0.06 – 0.33)	**>99%**	**>99%**
HR+/HER2-	**0.34** (0.19 – 0.48)	**0.13** (0.03 – 0.24)	**>99%**	**88%**

Nanda et al, ASCO 2017

Am I eligible for a clinical trial?

- Many clinical trials of novel ‘targeted’ agents
  - Often require testing tumor to see if target is present
- More efficient to test for multiple ‘targets’ at one time

MATCH master protocol (8/2015)



PRESENTED AT:

Single arm phase II trials (40 open & 8-9 planned this year)
~35 patients per treatment arm (>6000 screened to date)
GOAL: ORR > 25% & 6 mo PFS >35%
N=35- ORR>16% warrants further study & <5% null

The MATCH wasn't too hot

#101 , Krop et al.	#2503, Chae et al.	#100 Jhaveri et al.
Arm I: Taselisib PI3K mutated Non-breast/non-sq lung >/= 1 line of prior tx N=70	Arm W: AZD4547 FGFR1-3 amp/mutation/fusion N=50	ARM Q: TDM1 HER2 amplified (CN>7) Non-breast/non gastric N=35
ORR=0%	ORR=9.5%	ORR=8%

QUESTIONS:

Is the target viable?
Is the target viable across tumor types?
How best assess the target?
Does the drug hit the target?
Are there compensatory mechanisms that abrogate?
Is the drug too toxic?
Is the sample size adequate?

TAPUR: phase II prospective, multi-basket pragmatic trial

Solid tumors, MM, lymphoma
Progression on standard tx or none available

↓

Any CLIA-certified NGS

↓

Physician match to FDA-approved drug vs. MTB (no matches, multiple matches, general guidance)

↓

Central pharmacy provides drug →

Study Drug
Axitinib
Bosutinib
Cetuximab
Crizotinib
Dasatinib
Erlotinib
Nivolumab + ipilimumab
Olaparib
Palbociclib
Pembrolizumab
Regorafenib
Sunitinib
Temsirolimus
Trastuzumab + pertuzumab
Vemurafenib + cobimetinib
Vismodegib

GOAL: CBR=35%

Stage 1: 10 patients (2+ CBR)

Stage 2: 18 additional patients (7+ CBR)

**Analysis by genomic marker & tumor type*

N=1000; 12 expanded & 2 closed

Study Drug	Tumor Type	Variant
Expansion to stage two		
Cetuximab	Ovarian cancer	*KRAS*, *NRAS*, and *BRAF* wild type
Cobimetinib + vemurafenib	Colorectal cancer	*BRAF*_V600E/D/K/R mutation
Olaparib	Breast cancer Colorectal cancer	Germ line or somatic *BRCA1/BRCA2* inactivating mutations *ATM* mutation or deletion
Palbociclib	Head and neck cancer Soft tissue sarcoma Malignant neoplasm of bronchus and lung	*CDKN2A* loss or mutation *CDK4* amplification *CDKN2A* loss or mutation
Pembrolizumab	Breast cancer Colorectal cancer Uterine cancer	High tumor mutational burden High tumor mutational burden High tumor mutational burden
Pertuzumab + trastuzumab	Colorectal cancer	*ERBB2/ERBB3* mutation, amplification, or overexpression
Sunitinib	Breast cancer	*FGFR1* mutation or amplification
Closed at stage one		
Palbociclib	Pancreatic cancer Malignant neoplasm of gallbladder and bile ducts	*CDKN2A* loss or mutation

JCO Precision Oncology 2018

Tumor testing – beware

2016: 77 y/o man metastatic NSCLCa

- Tumor testing to determine therapy
- FHx-father with prostate cancer at 63
- Patient recommended chemo

2018:

- Granddaughter presents with stage 4 ovarian cancer
- Germline BRCA 2 carrier
- Grandfather's NGS test: somatic BRCA2 mutation

Questions:

- Should the patient have been counseled about finding?
- Should confirmatory germline testing have been performed?

High frequency of germline mutations for cancer patients found during tumor testing

Heterogeneous group with stage 4 disease
variable age, tumor types, pedigree

Series	Testing type	n	Frequency
MSKCC-IMPACT (JAMA-Onc 2016)	Panel	1566	12.6%
MDACC (Annals of Oncology 2016)	Panel	1000	4.3%
UNC (Clin Cancer Res 2016)	Panel	439	4.3%
U. Michigan (ASCO 2017)	WGS	500	12.2%
Indiana University (ASCO 2017)	WGS	139	5%
TCGA (Cell 2018)	WES	10,389	8%

Research

JAMA | Preliminary Communication

Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing

Diana Mandelker, MD, PhD; Liying Zhang, MD, PhD; Yelena Kemel, MS, ScM; Zsofia K. Stadler, MD; Vijai Joseph, PhD; Ahmet Zehir, PhD;

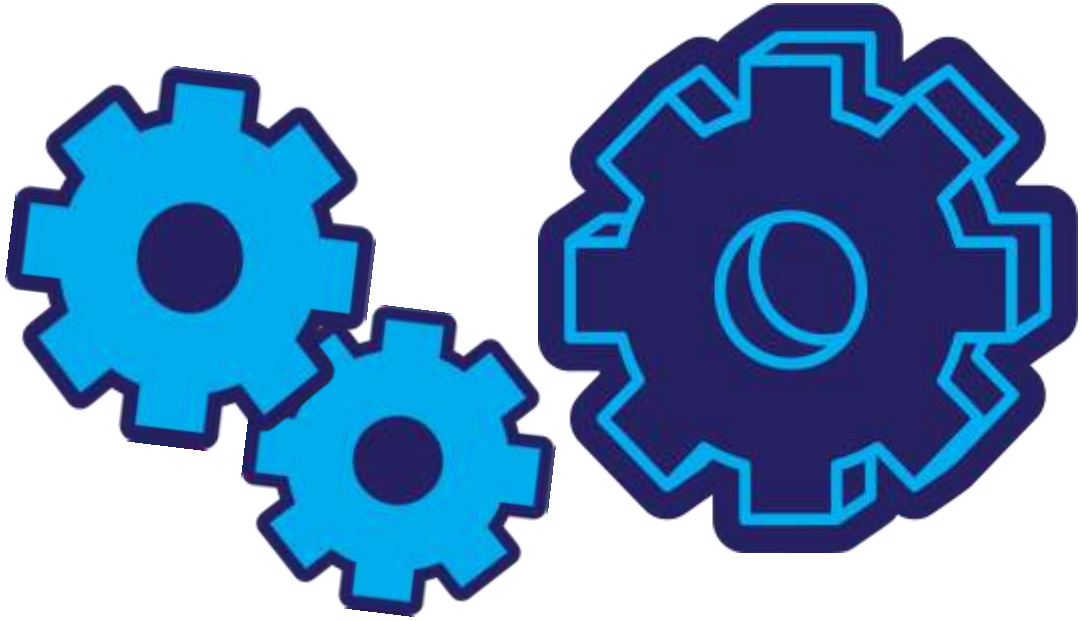
Should all cancer patients have germline genetic testing?

- **MSKCC IMPACT (n=10,336)**
  - 1040 patients referred for germline analysis
    - Formal pedigree
  - 17.5% germline mutation

>50% (9.7%) would not have been tested using clinical guidelines

Incidental Germline Mutations: This is a shared problem!

- **Testing providers:** Provide clear recommendations based on platform & gene/variant coverage
- **Care providers:** Pay attention & provide counseling
- **Payers:** Cover confirmatory testing in absence of pedigree



Future

- Further refinement of initial treatment
- Individualized therapy
  - Failure of current testing to improve outcome in metastatic disease isn't the tests fault
- Tumor DNA in plasma
  - Serial monitoring ->what has changed
- Reduced cost
- Population-based genetic testing
  - Current guidelines miss ~50% of families

Thanks!

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