Facciamo il punto su...

Utilizzo della genetica nella personalizzazione dei percorsi diagnostico-terapeutici:

nuovi geni ad alta-moderata penetranza

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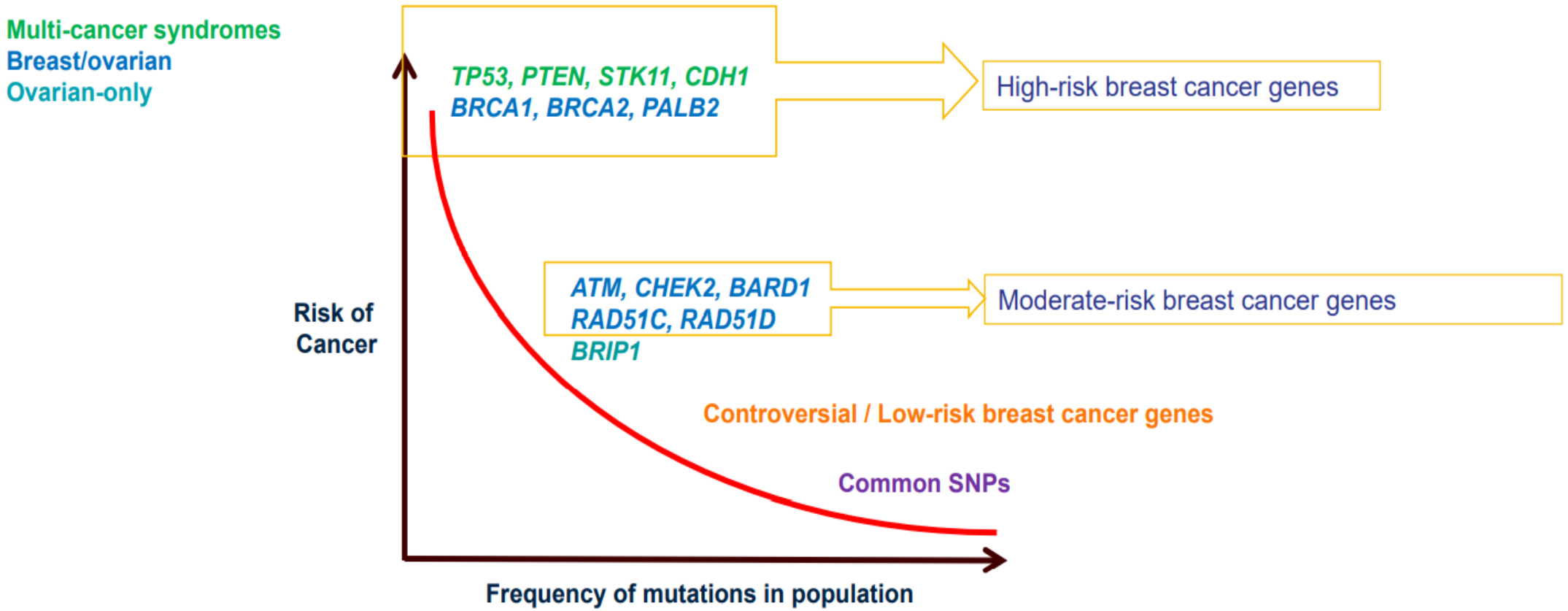
CTF MO

Multiple germline genetic variants increase the risk of breast cancer



2022: Genes associated with breast cancer

Risk	Genes
HIGH (>4-fold)	*BRCA1* *BRCA2* *PALB2* *CDH1, PTEN, STK11, TP53*
MODERATE (2- to 4-fold)	*BARD1* *CHEK2* *RAD51C* *RAD51D* *ATM*
LOW (1- to 2-fold) or Controversial	*NF1* *MSH6* *FANCC* *FANCM*
NO ASSOCIATION	*APC, BLM, BRIP1, CDKN2A, NBN, MLH1, MRE11A, MSH2, PMS2, RAD50, XRCC2, MUTYH, ABRAXAS1, AKT1, BABAM2, EPCAM, GEN1, MEN1, PIK3CA, RECQL, RINT1*

High-Moderate Penetrance Hereditary Syndromes

SYNDROME	TUMORAL SPECTRUM	TRANSMISSION	GENES
BREAST/OVARY	Breast, ovary, uterus, prostate, stomach, colo-rectum, pancreas, bilious tract, melanoma	Dominant autosomal	BRCA 1 BRCA2
LI-FRAUMENI	Soft tissues, breast, bone, leukemya, brain, adrenal	Dominant autosomal	P53
COWDEN	Breast, tyroid, endometrium (amartomes)	Dominant autosomal	PTEN
Diffuse Gastric Cancer	Stomach, Lobular Breast	Dominant autosomal	CDH1
PEUTZ-JEGHERS	Colo-rectum, stomach, ovary, testis, cervix, pancreas, breast	Dominant autosomal	LKB1
PALB2	Breast, FA, ovary, pancreas	Dominant autosomal	PALB2
ATM	Breast, stomach, pancreas Ataxia Teleangectasia	Dominant autosomal Recessive autosomal	ATM
CHEK2	Breast, Colo-rectum, Prostate, Thyroid, Kydney	Dominant autosomal	CHK2

[1]*Cortesi L. Exp Opinion 2021*

Breast Cancer in High Penetrance Risk

	Starting age surveillance	MX	MRI	RRM
TP53	20 y	30-75 y.annually	20-75 y annually	Discuss with individual
PTEN	25 y	30-75 y. annually	25-75 y. annually	Discuss with individual > 25
CDH1	30 y	30-65 y annually	30-65 y annually	Consider on FH
STK11	25 Y	30-59 y annually	25-59 y annually	Discuss with individual
PALB2	25 y	30-65 y annually	25-65 y annually	Consider on FH

Nielsen S et al., JCO Precision Oncol 2018

Panel 1: 2016 version of the surveillance protocol for individuals with germline *TP53* pathogenic variants

Children (birth to age 18 years)

Adrenocortical carcinoma

- Ultrasound of abdomen and pelvis every 3–4 months
- Blood tests every 3–4 months:* 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione
- 24 h urine cortisol, if feasible

Brain tumour

- Annual brain MRI

Soft tissue and bone sarcoma

- Annual rapid whole-body MRI

Leukaemia or lymphoma

- Blood tests every 3–4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

General assessment

- Complete physical examination every 3–4 months, including anthropometric measurements plotted on a growth curve (with particular attention to rapid acceleration in weight or height), signs of virilisation (pubic hair, axillary moisture, adult body odour, androgenic hair loss, clitoromegaly, or penile growth), and full neurological assessment
- Prompt assessment with primary care physician for any medical concerns

Adults

Adrenocortical carcinoma (age 18–40 years)

- Ultrasound of abdomen and pelvis every 3–4 months
- Blood tests every 3–4 months:* 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, and androstenedione
- 24 h urine cortisol, if feasible

Breast cancer

- Monthly breast self-examination (age 18 years onwards)
- Clinical breast examination twice a year (age 20–25 years onwards, or 5–10 years before earliest known breast cancer in the family [whichever comes first])
- Annual mammography† and breast MRI screening‡ (age 20–75 years, or 5–10 years before earliest known breast cancer in the family [whichever comes first])
- Consider risk-reducing bilateral mastectomy

Brain tumour (age 18 years onwards)

- Annual brain MRI

Soft tissue and bone sarcoma (age 18 years onwards)

- Annual rapid whole-body MRI‡
- Ultrasound of abdomen and pelvis every 3–4 months

Colorectal cancer

- Colonoscopies every 2 years (start at age 25 years, or 10 years before earliest known colon cancer in the family [whichever comes first])

Melanoma (age 18 years onwards)

- Annual dermatological examination

Leukaemia or lymphoma (age 18 years onwards)

- Blood tests every 3–4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

General assessment

- Complete physical examination every 3–4 months
- Prompt assessment with primary care physician for any medical concerns

*Serial specimens obtained at the same time of day and processed in the same laboratory. †Breast ultrasound with mammography as indicated by breast density, but not instead of breast MRI or mammography. ‡Breast MRI to alternate with annual rapid whole-body MRI (one scan every 6 months).

Villani A. et al, Lancet Oncol 2016

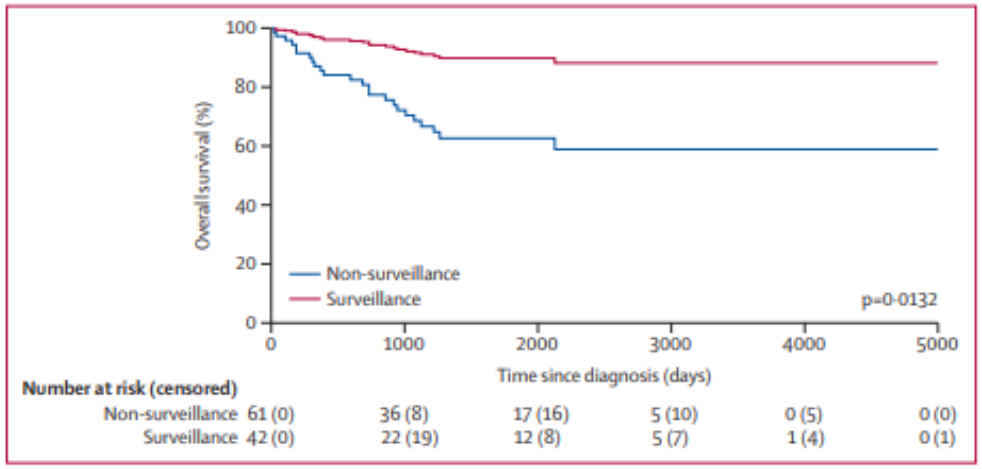
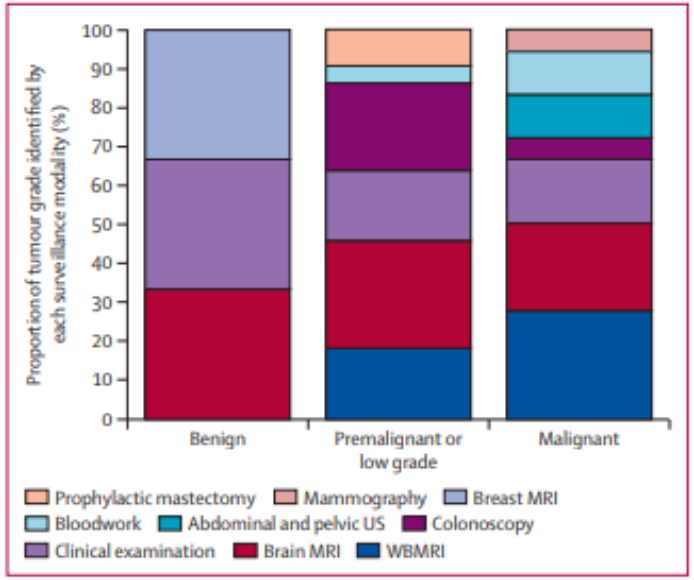


Figure 1: **Overall survival in the surveillance and non-surveillance groups**
Number at risk refers to the number of tumours, not individuals.



Panel 2: **Tumours detected by the surveillance protocol, classified by grade**

Benign

- Thyroid adenoma
- Breast fibroadenoma
- Meningioma

Premalignant or low grade

- Myelodysplastic syndrome
- Osteochondroma (three patients)
- Ductal carcinoma in situ (three patients)
- Low-grade glioma (six patients)
- Colonic or rectal adenoma (five patients)
- Dysplastic naevus
- Melanoma in situ
- Squamous cell carcinoma
- Thyroid Hürthle cell adenoma

Malignant

- Malignant fibrous histiocytoma (two patients)
- Osteosarcoma
- Adrenocortical carcinoma (three patients)
- Invasive ductal carcinoma
- Breast cancer (chest wall)
- Choroid plexus carcinoma (two patients)
- Chordoma
- Ependymoma
- Colorectal carcinoma (two patients)
- Lung carcinoma

Tumours are in one patient unless otherwise stated. Does not include two interval tumours missed by the surveillance protocol.

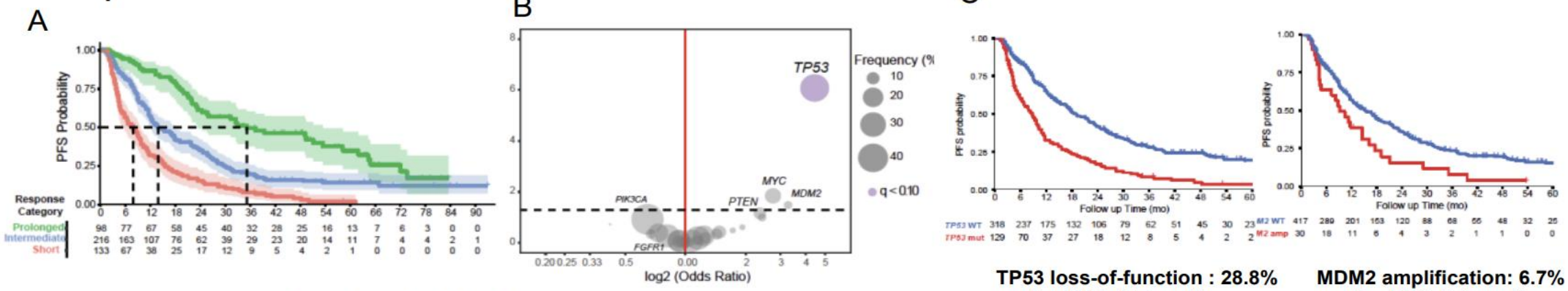
Villani A. et al, Lancet Oncol 2016

TP53 Breast Cancer Characteristics

Author	Year	*TP53* carriers with BC N	HER2 positive tumors N	Other findings
Wilson JRF et al [56]	2010	12*	10* (83%)	–
Melhem-Bertrandt A et al [57]	2012	30	20 (67%)	–
Masciari S et al [58]	2012	32*	20 (63%)	–
Bakhuizen JJ et al [33]	2019	8	5 (63%)	–
Packwood K et al [59]	2019	36	20 (56%)	–
Le A et al [60]	2020	38*	22 (58%)	–
Alyami H et al [61]	2021	21*	10 (53%)	2 cases of malignant phyllodes tumor
Kuba MG et al [62]	2021	17	9 (53%)	2 cases of HER2 negative BC by IHC (1 +) but positive by FISH.
Rippinger N et al [63]	2021	32	11 (34%)	10 cases (31.3%) of luminal B-like BC
Breast Cancer Association Consortium, Mavaddat N et al [34]	2022	51	NR (46%)	OR for HER2 + BC 7.14 (95%CI 3.34–15.28)
Sandoval RL et al [64]	2022	87	32 (41%)	43 cases (55%) of luminal-like BC

Blondeaux E et al., Cancer Treat Review 2023

(1) *TP53* loss-of-function variant and *MDM2* amplification affect the long-term response

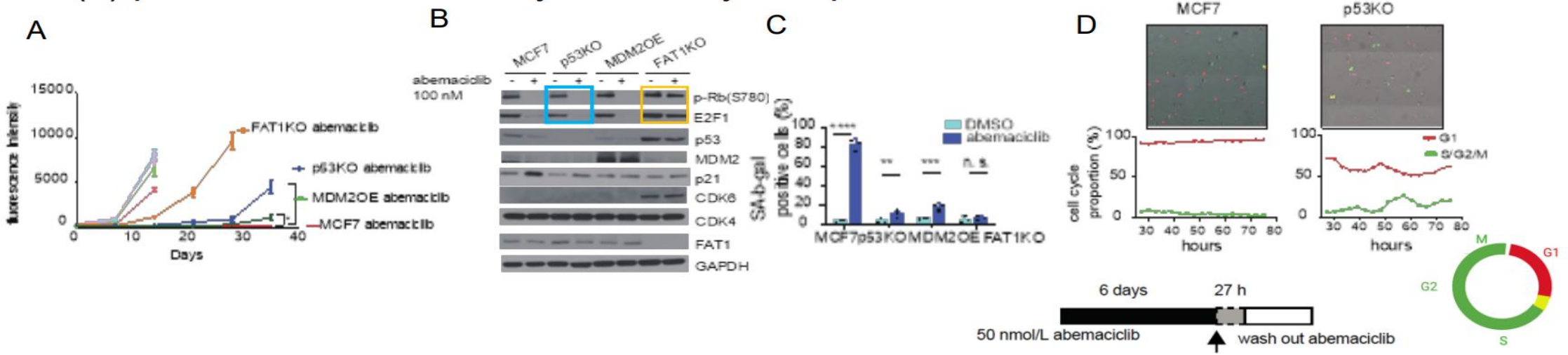


447 patients with first-line CDK4/6i

TP53 loss-of-function : 28.8%
median PFS: 8.7 months

MDM2 amplification: 6.7%
median PFS: 9.1 months

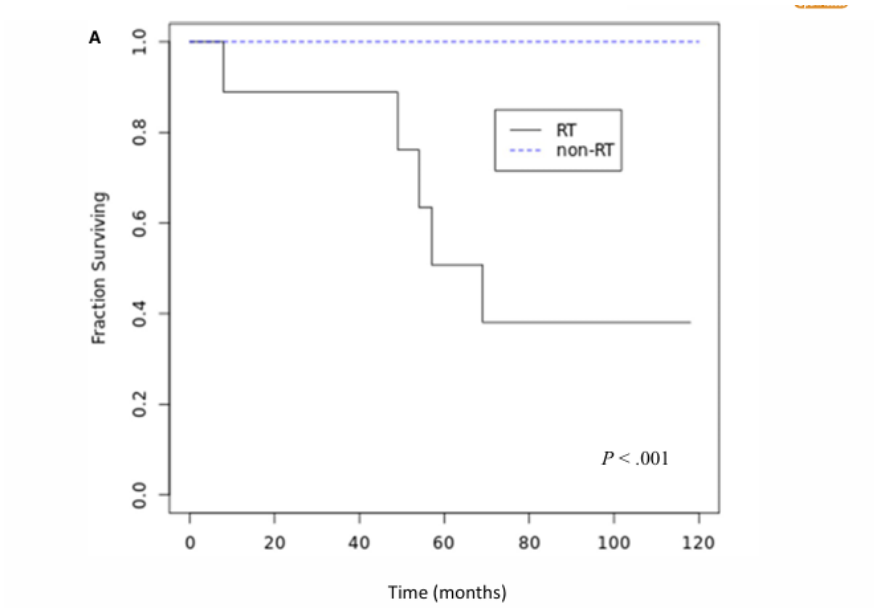
(2) p53 loss enables cell cycle reentry and prevents senescence



Kudo R, SABCS 2023

Radiation therapy and secondary malignancy in LFS

	Non-RT n = 24	RT n = 9	*P*-value
Subsequent malignancy (# of pts)			
Recurrent disease (same histology)			
Local	1	3	
Distant/Metastasis	0	0	
New primary (different histology)			
Local	0	0	
Distant	10	2	
Total	11 (45.8%)	5 (55.5%)	.7080



Numbers at risk

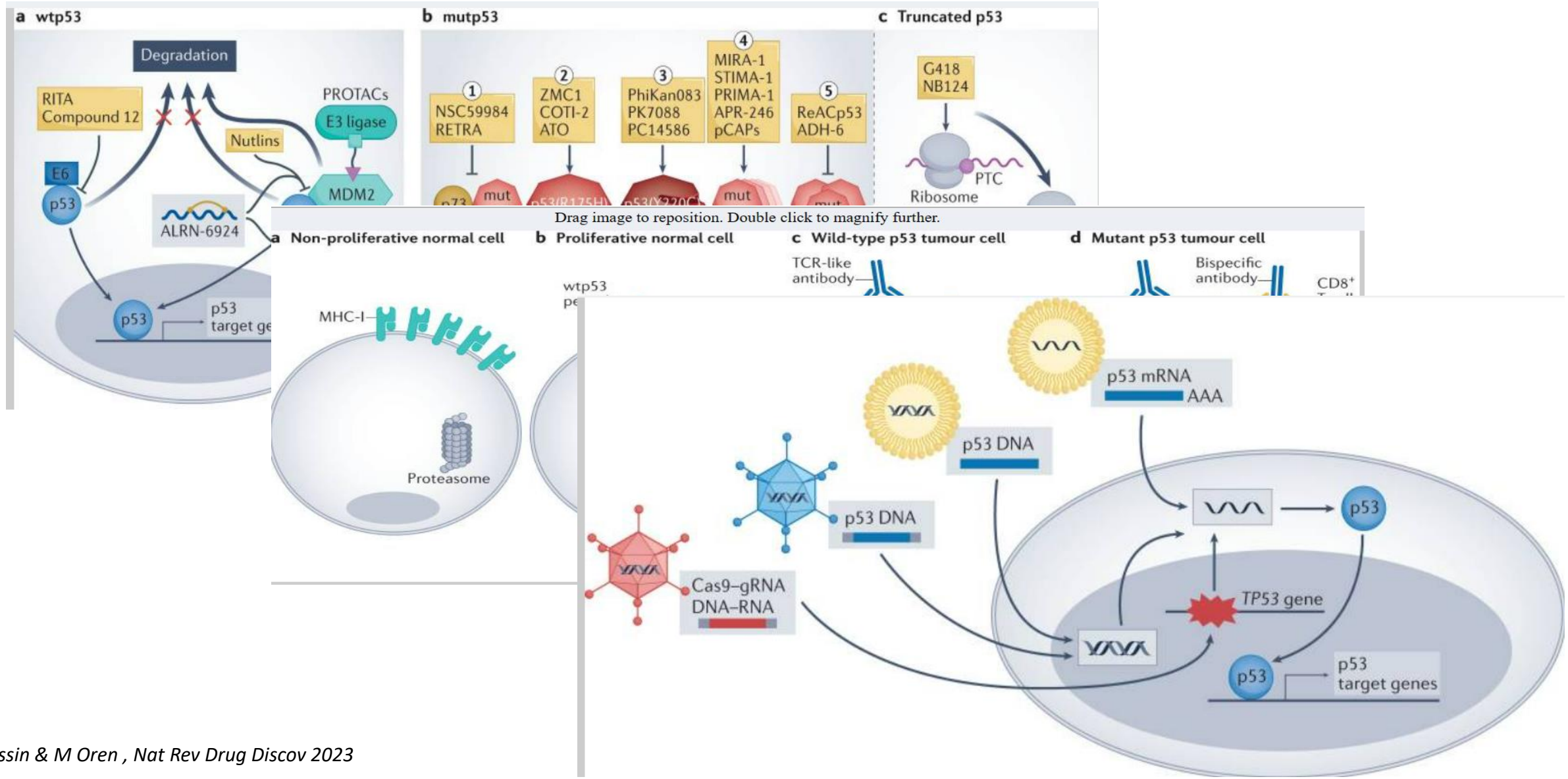
	0	20	40	60	80	100	120
RT	9	8	7	4	3	1	0
Non-RT	24	21	16	12	11	9	7

"We recommend that RT should be considered as part of the treatment algorithm when clinically indicated and after multidisciplinary discussion"

All five deaths in RT group were due to cancer progression

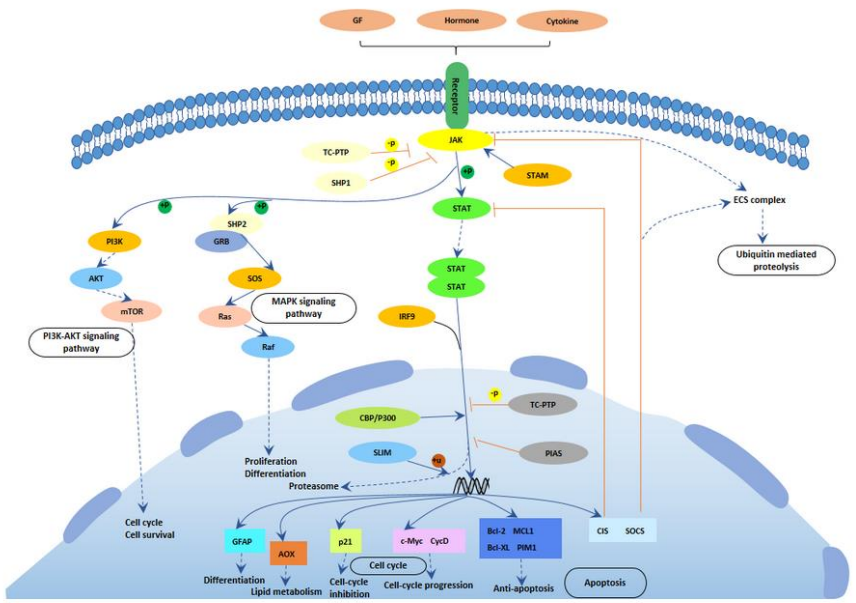
G. Hendrickson et al., Cancer Med 2020

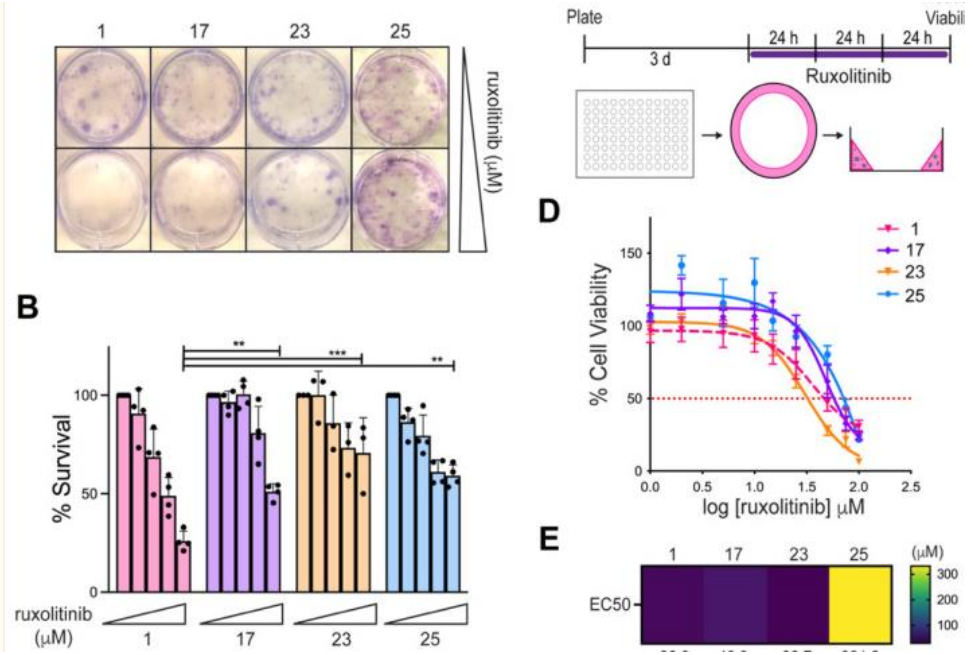
Drugging p53 in cancer: one protein, many targets



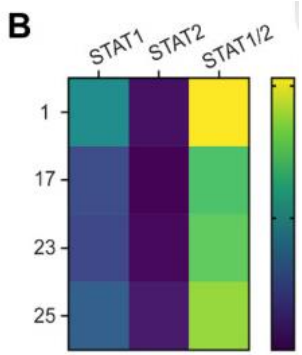
O Hassin & M Oren , Nat Rev Drug Discov 2023

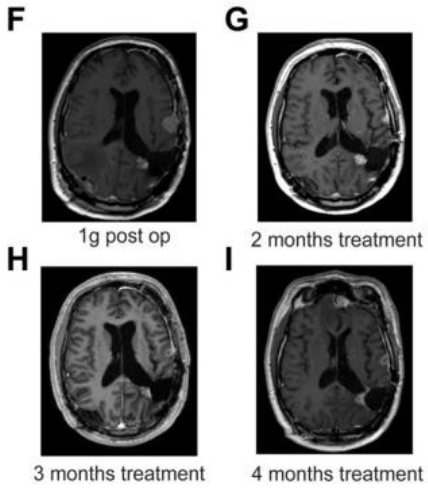
Li Fraumeni Syndrome and STAT





A				
Patient ID	1	17	23	25
Gender	Male	Male	Female	Female
Age	24	71	46	46
IDH	Wildtype	Wildtype	Wildtype	Wildtype
MGMT	Wildtype	Wildtype	Wildtype	Wildtype
TP53	Germline Mutant	Wildtype	Somatic Mutant	Somatic Mutant
EGFR	Wildtype	Wildtype	Amplification	Wildtype
Drug target	JAK/STAT1	MDM2	JAK1	CDK4



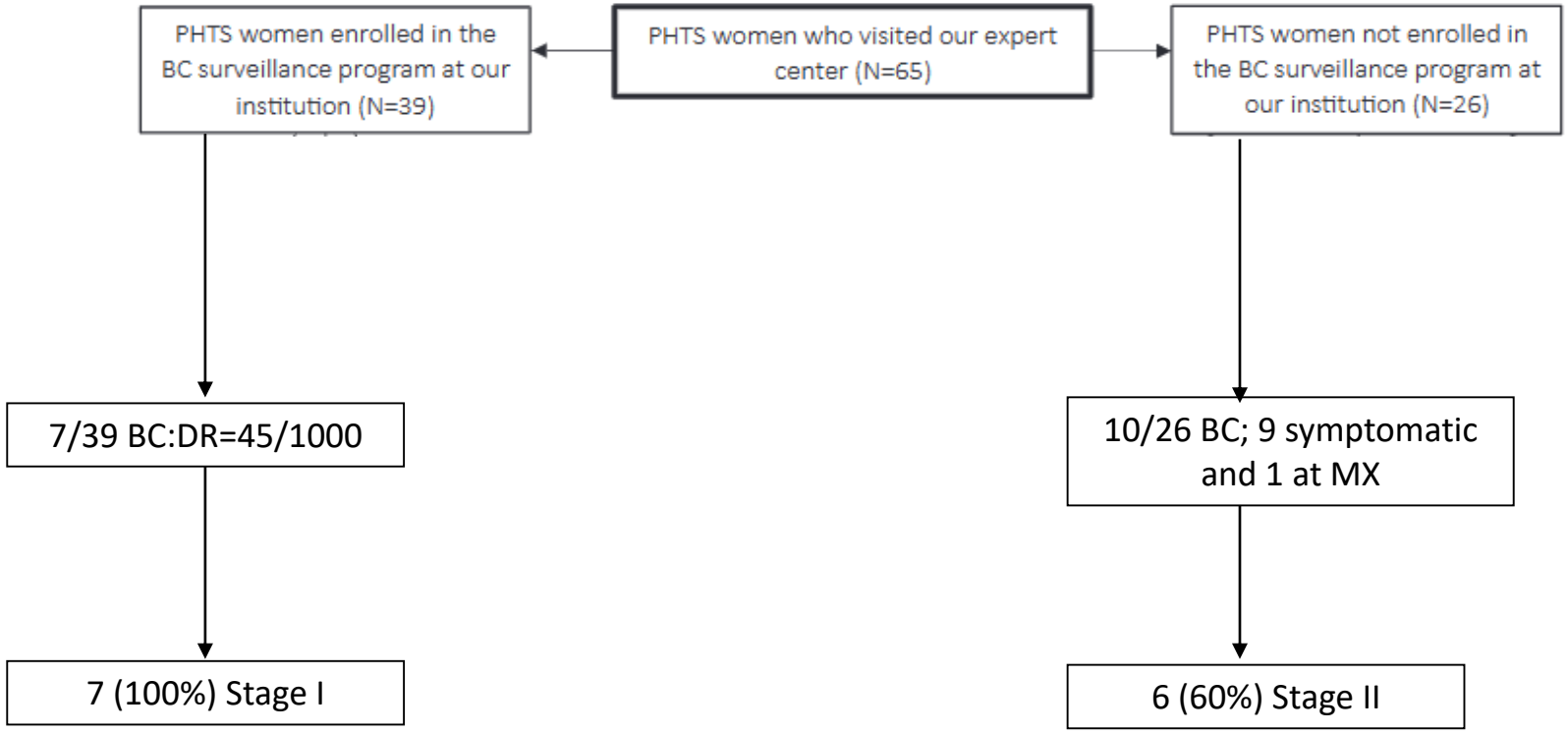


Reed M et al., Cells 2021

Cowden Syndrome Cancer Risks

Tumor Site	Risk Pilarski R. JGC.2009;18:13-27	Risk Tan et al. Clin Can Res. 2012;18(2):400-7
Breast	25-50%	85%
Thyroid	3-10%	35%
Endometrial	5-10%	28%
Renal Cell	Unknown	34%
Melanoma	Unknown	6%
Colon	Unknown	9%

The yield and effectiveness of breast cancer surveillance in women with PTEN Hamartoma Tumor Syndrome



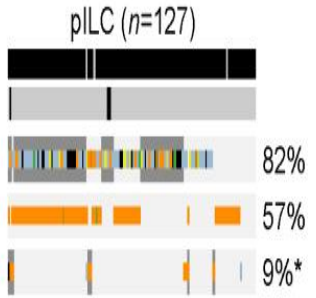
Hoxhaj DX et al., Cancer 2022

Hereditary Diffuse Gastric Cancer

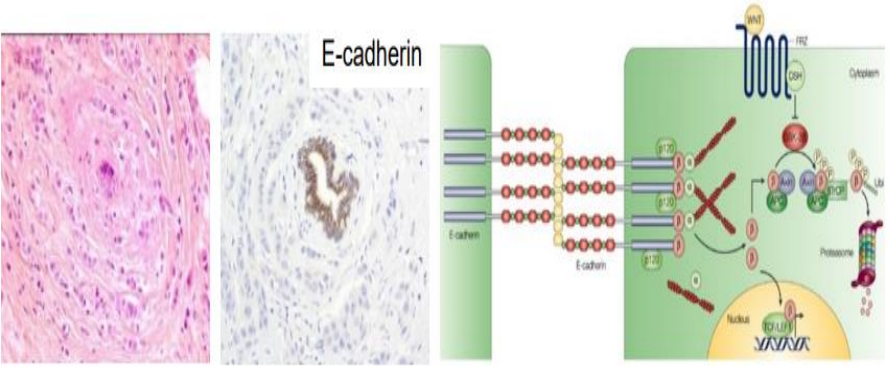
Cancer Type	Age Range	Cancer Risk	Risk for General Population
Gastric (male)	To age 80	67-70%	0.6%
Gastric (female)	To age 80	56-83%	0.6%
Female Breast	To age 50	10%	1.9%
	To age 80	39-52%	10.2%
Colorectal	To age 80	Possible Increased Risk	3.0%

Invasive Lobular Carcinoma

- Most frequent breast cancer special histologic subtype
- Distinctive phenotype
- *CDH1* bi-allelic inactivation



CDH1 – E-cadherin LOF mutations

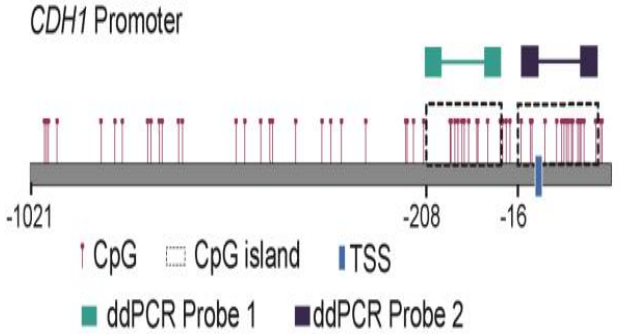


Mechanisms:

- Bi-allelic mutation
- Homozygous deletion
- Promoter methylation

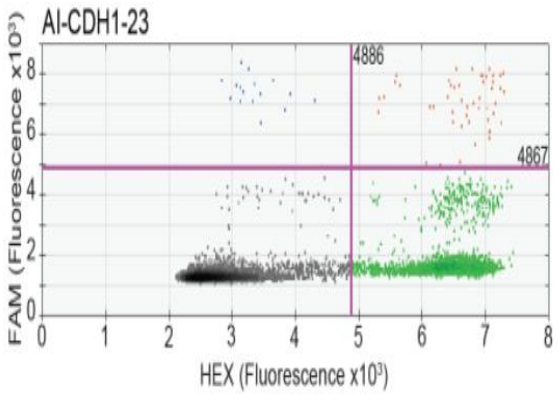
Ciriello et al, Cell 2015; Pareja et al, NPJ Breast Cancer 2020; Lee et al, Clin Cancer Res 2018

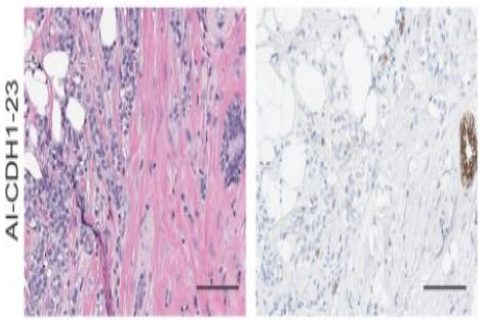
Alternative Mechanisms of *CDH1* Inactivation: Epigenetic Silencing



***CDH1* promoter methylation:**

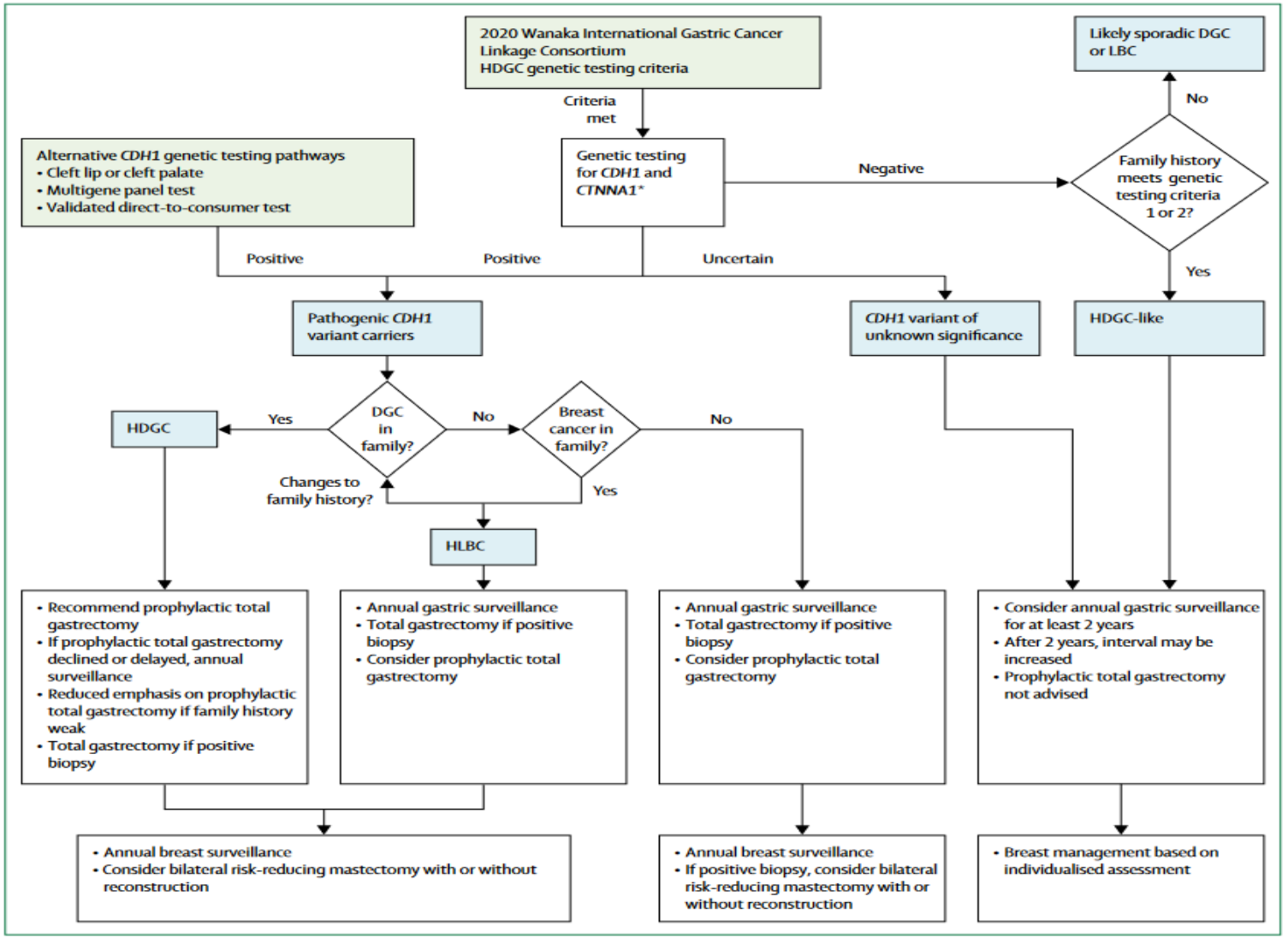
18/28 (64%) of cases interrogated





CDH1 promoter methylation is prevalent in ILCs lacking CDH1 pathogenic mutations

Hereditary diffuse gastric cancer: updated clinical practice guidelines



Blair VR et al., Lancet Oncol 2020

❑ The High Risk Rare Genes

PTEN

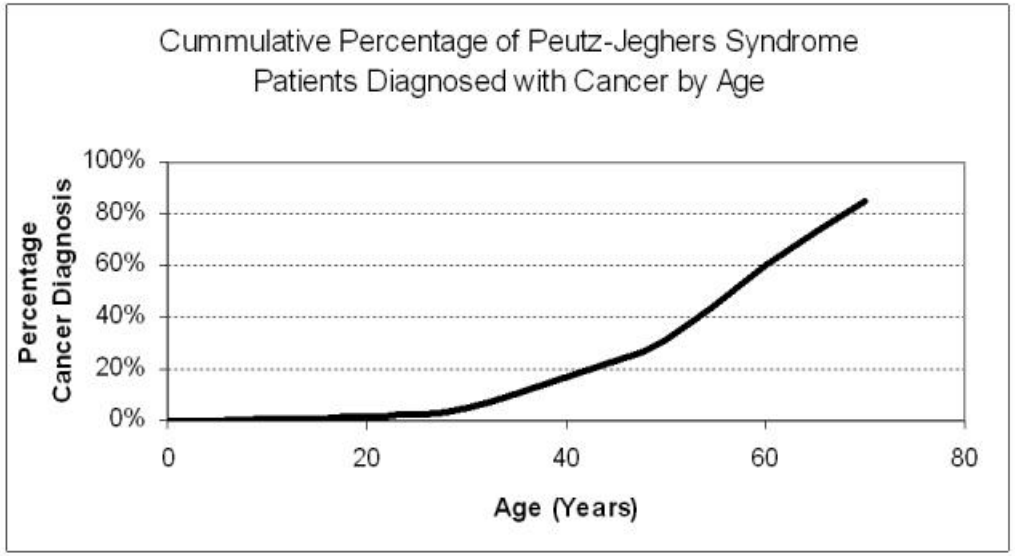
- PTEN Hamartoma Tumor syndrome (PHTS) encompasses a clinical spectrum of heritable disorders including Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome, and Proteus and Proteus-like syndrome
- **Breast cancer risk estimates (67–85 %) for women with germline PTEN mutations** are similar to those quoted for patients with germline mutations in the BRCA1/2 genes
- **MRI surveillance or Prophylactic IRRM or CLRRM should be discussed**

CDH1

- **Bilateral LBC with or without family history of LBC, with age at onset < 50 years; and (B) unilateral LBC with family history of LBC, with age at onset < 45 years.**
- Following the above-mentioned clinical criteria, a CDH1 germline mutation could be identified in 3% of the screened population
- **MRI or Prophylactic IRRM or CLRRM should be discussed**
- Diffuse HGC should be screened – Prophylactic Total Gastrectomy needs to be discussed

Peutz-Jeghers Syndrome

- Pancreatic Cancer
- Liver
- Lung
- Breast
- Ovary
- Uterine Cancer
- Testis
- Others



The management of Peutz-Jeghers Syndrome:EHTG guidelines

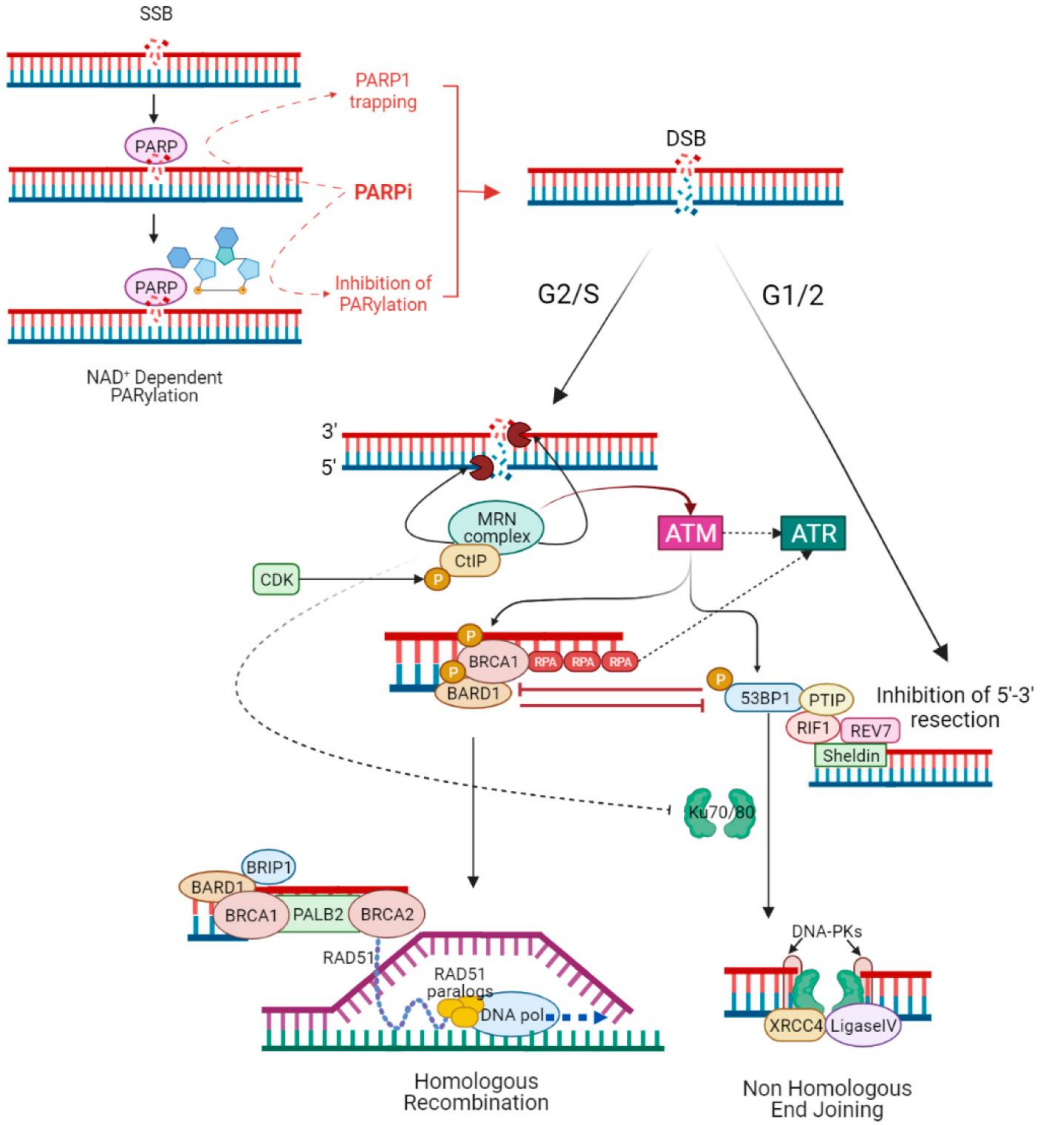
The following breast surveillance is recommended in female PJS patients: Raising awareness at age 18 years e.g., by starting breast self-examination; Clinical breast exam every 6–12 months starting at age of 25 years; Annual breast contrast MRI screening (or breast ultrasound if MRI contraindication or unavailability) at age 25–30 years; Annual mammogram with consideration of tomosynthesis and ultrasound for dense breast and annual breast contrast MRI at age 30–50 years; Annual mammogram with consideration of annual breast contrast MRI for dense breast pattern at age 50–75 years; Management should be considered on an individual basis from age > 75 years.
Level of evidence: low
Strength of recommendation: moderate

The optimal breast surveillance strategy in female PJS patients remains debated and the benefits of surveillance remain to be established. Therefore, it is recommended that surveillance is conducted at centers of expertise in the framework of a study or registry.
Level of evidence: low
Strength of recommendation: strong

As evidence for its benefit is lacking, prophylactic mastectomy is currently not recommended for female PJS patients. Risk reducing mastectomy should be discussed in a multidisciplinary setting also taking into account family history and other clinical factors.
Level of evidence: low
Strength of recommendation: moderate

Wagner A et al., J Clin Med 2021

DNA double-strand break repair mechanisms

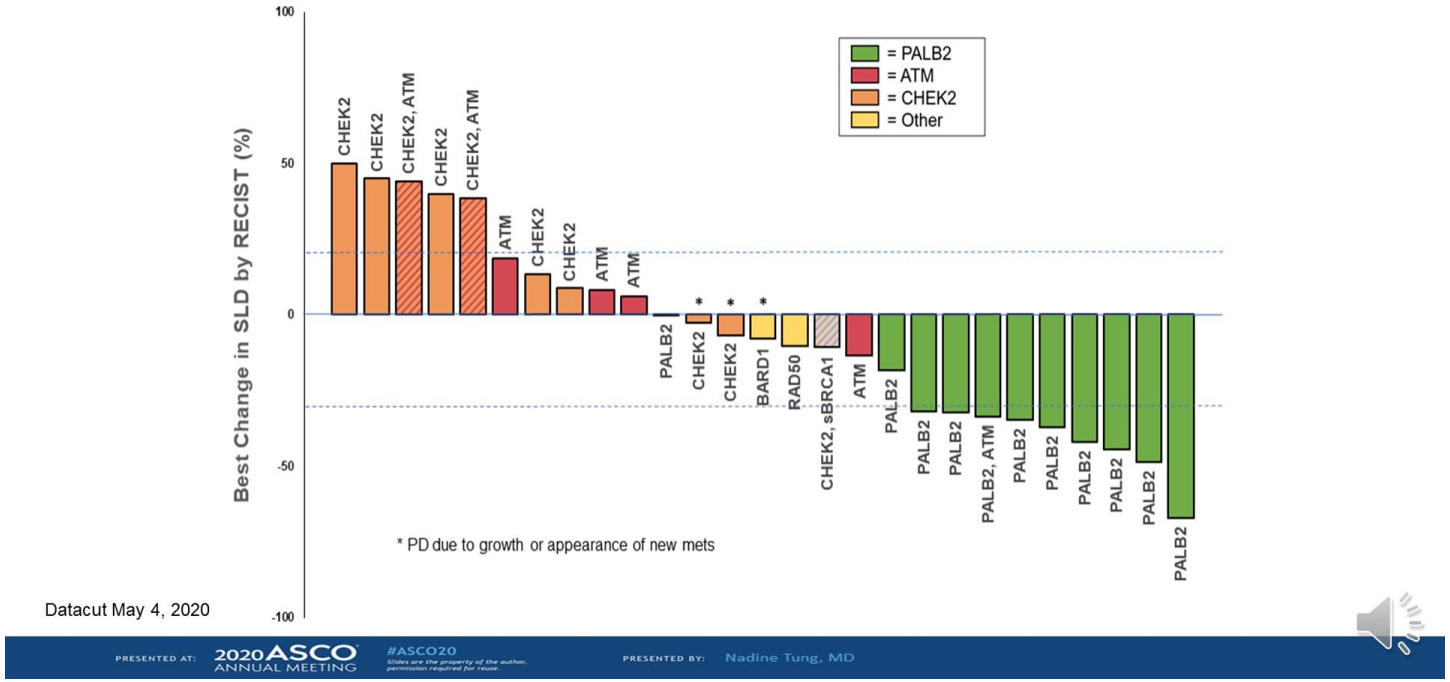


GENOMIC INSTABILITY

Cell death

Piombino C, Cortesi L. Cancers 2022

Best Overall Responses: Cohort 1 (Germline)

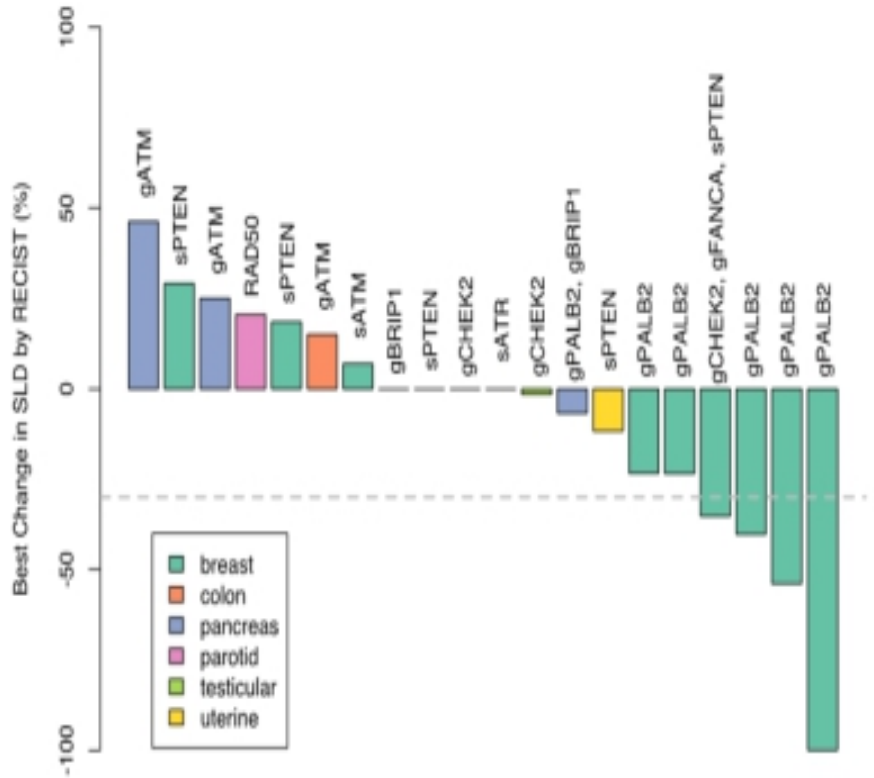


Nadine Tung et al., JCO 2020

Talazoparib Beyond BRCA cohort B

Best Overall Responses

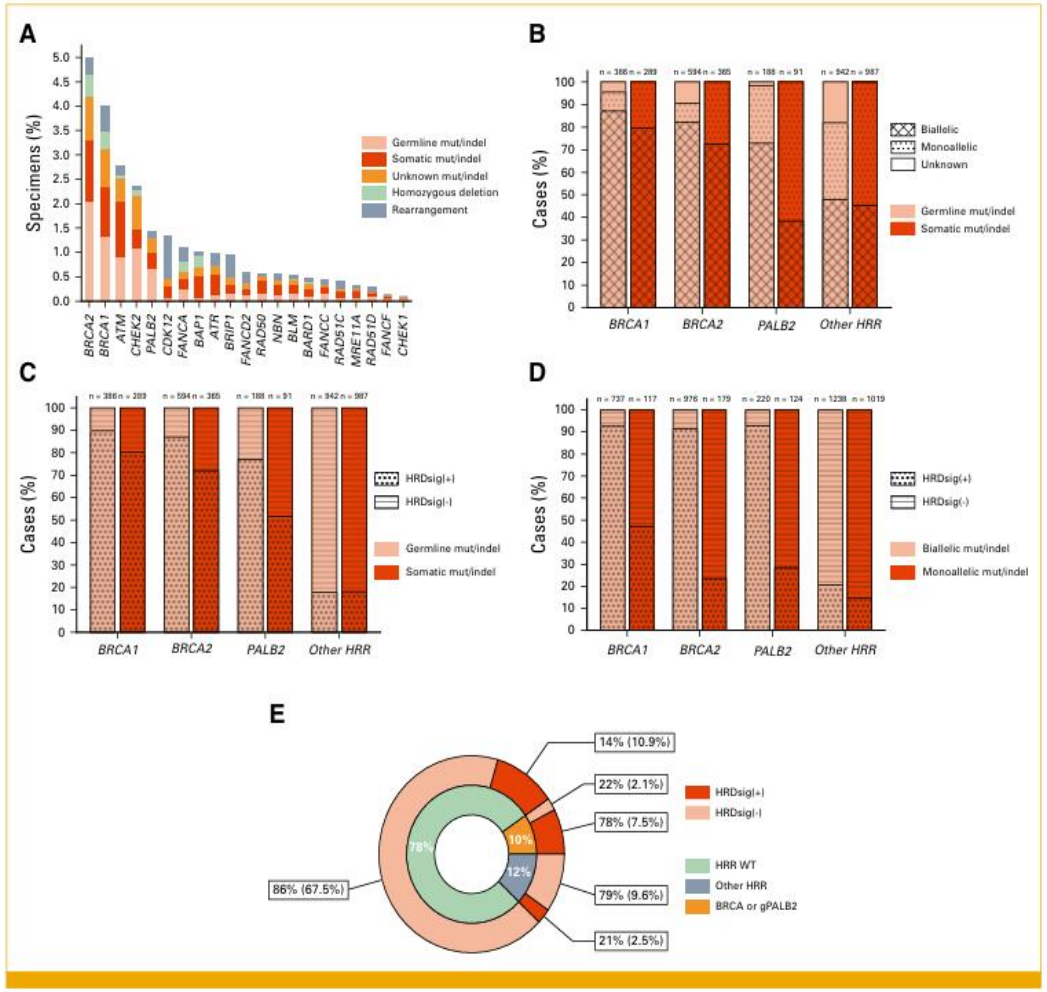
All Patients

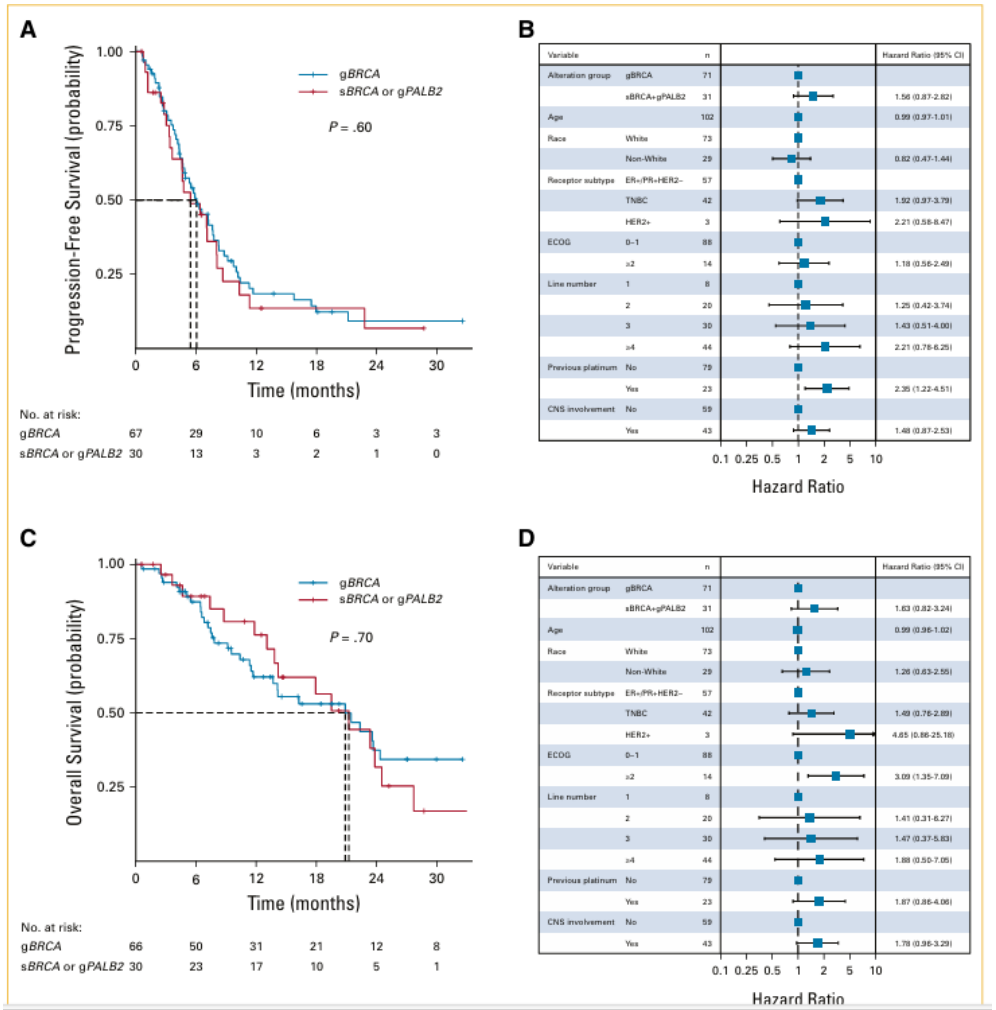


Joshua Gruber, MD, PhD

SECONDARY OBJECTIVES:

- To evaluate the safety of talazoparib in subjects w advanced PALB2 mutation-associated cancer.
- To evaluate the progression-free survival (PFS) of talazoparib monotherapy in subjects with advanc PALB2 mutation-associated cancer.
- To evaluate the clinical benefit rate (CBR) of talazoparib monotherapy in subjects with advanc PALB2 mutation-associated cancer.
- To evaluate the ability of ctDNA to identify and characterize the nature of PALB2 mutations at baseline and upon progression in subjects with advanced PALB2 mutation-associated cancer trea with talazoparib monotherapy.

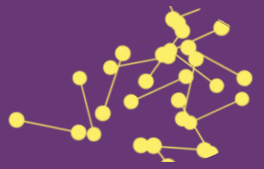




Batalini F., JCO Prec Oncol 2023

Opportunities of a PARP1 selective inhibitor and trapper

First generation PARPi are dual PARP1-PARP2 inhibitors/DNA-trappers



PARP2 has been linked to hematological toxicity, the main clinical toxicities observed with first generation PARPi[3]

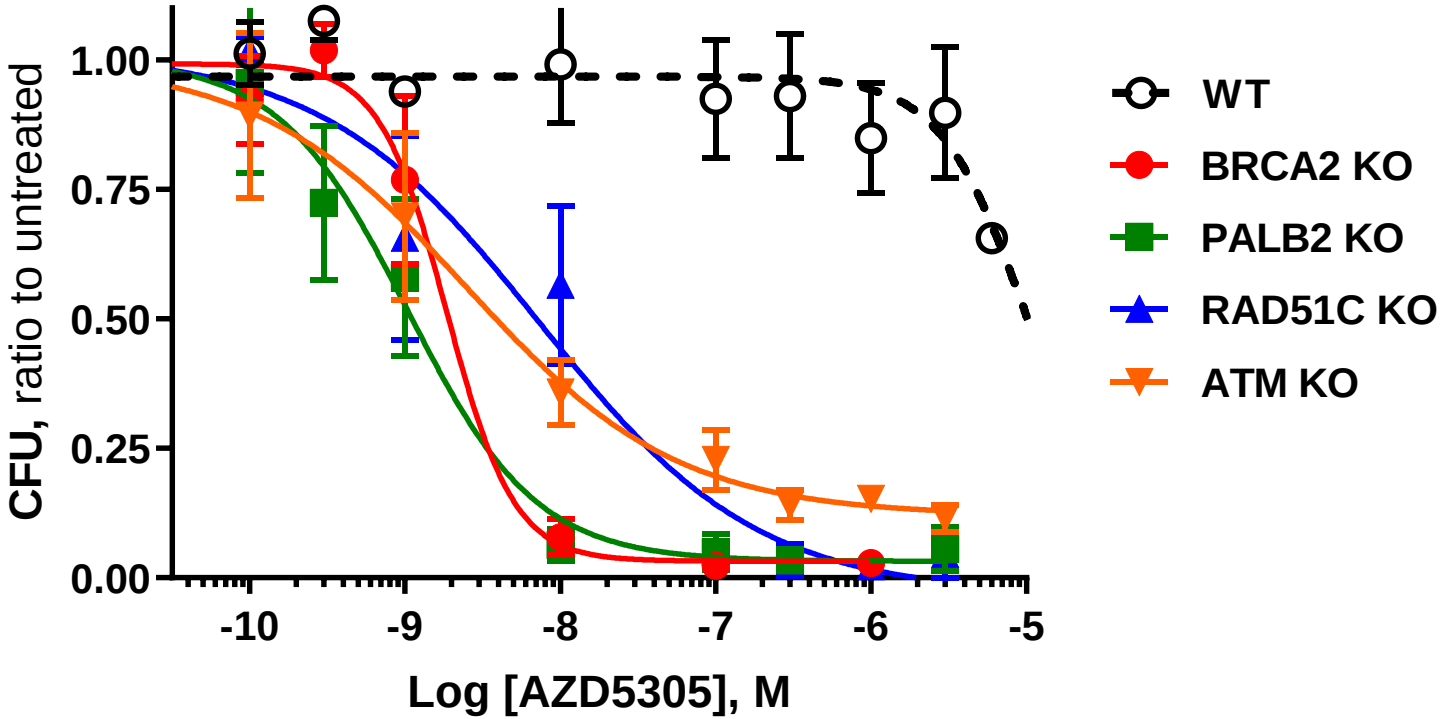
A selective PARP1 inhibitor and DNA trapper may improve the therapeutic index vs. first generation PARPi

1. Murai, J. et al. *Cancer Res* 2012;72(21):5588–5599; 2. Ronson GE, et al, *Nat Commun.* 2018;9(1):746. 3. Farrés J, et al. *Blood* 2013;122(1):44–54

AZD5305 potently inhibits proliferation in cancer cell lines “beyond BRCAm”

AZD5305 GI_{50} in isogenic cells for other HRR genes

Clonogenic assay in SKOV-3 background



Cell line:	AZD5305 GI50 (nM)
WT	30,000
BRCA2 KO	2
PALB2 KO	1
RAD51C KO	7
ATM KO	5

Mean of 4 independent experiments

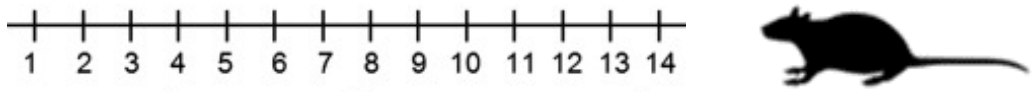
AZD5305 treatments lead to low nM GI_{50} in the HRD cells; double-digit mM in the wt isogenics.

AZD5305 has also minimal effects in non-cancer cells (MCF10-A)

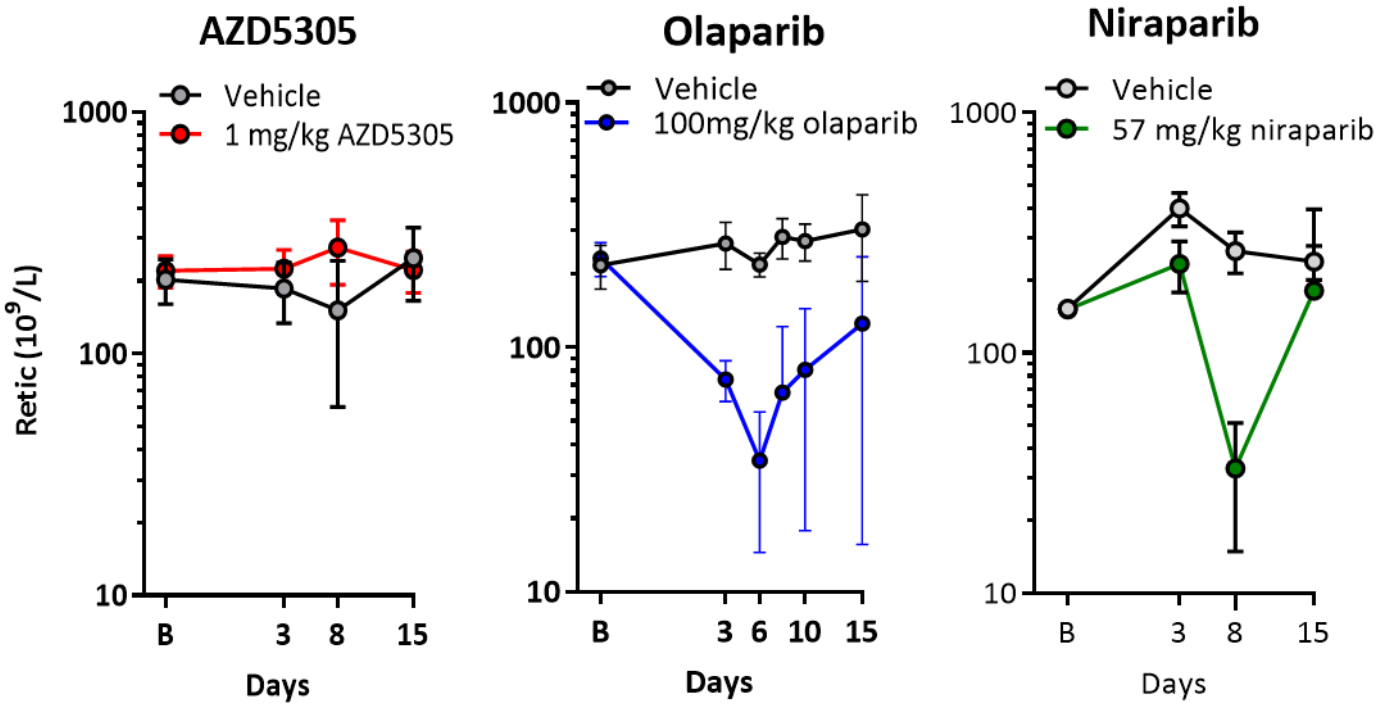
1. Illuzzi G et al., Clin Cancer Res. 2022 28:4724-4736 2. Zheng J et al., Front Pharmacol. 2023 13:979873 3. Dellavedova G et al., Cancer Res Commun. 2023 3:489-500

No haemato-toxicity was observed with AZD5305 treatments in vivo

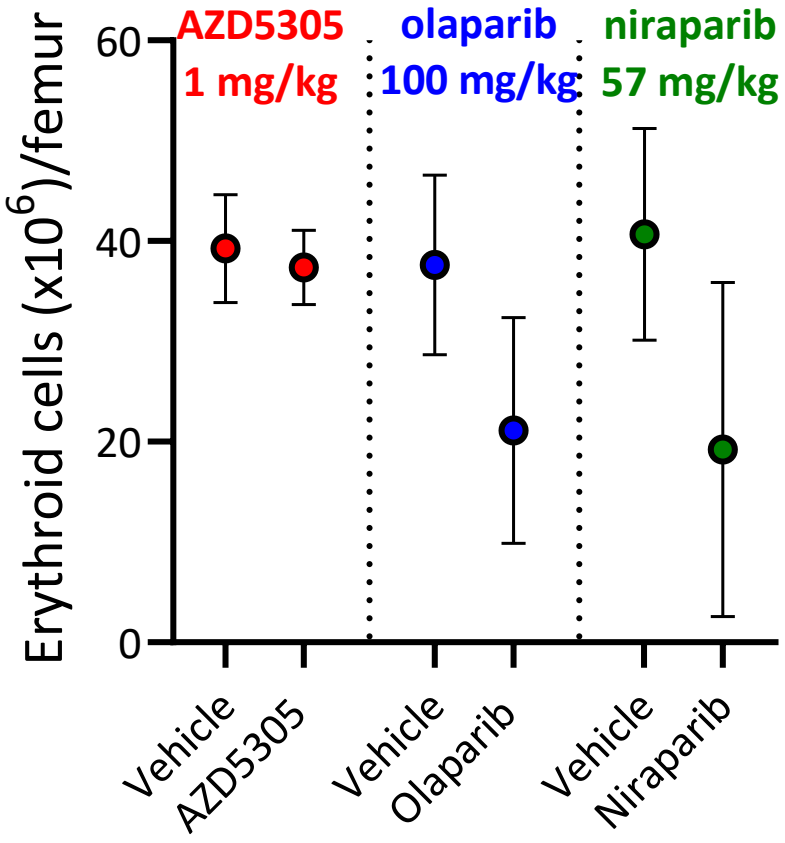
Rats were tested at matched exposure of PARPi



Reticulocytes



Erythroids



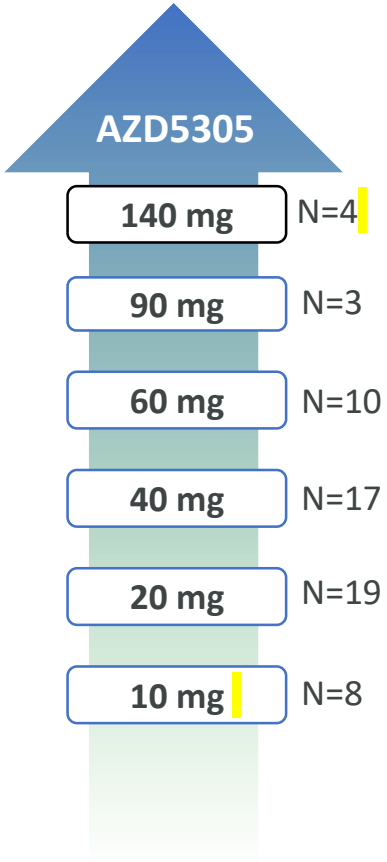
Neutrophils and platelets were also unaffected with AZD5305

1. *Illuzzi G et al., Clin Cancer Res. 2022 28:4724-4736 2. Zheng J et al., Front Pharmacol. 2023 13:979873 3. Dellavedova G et al., Cancer Res Commun. 2023 3:489-500*

PETRA is the first in-human Phase I/II study investigating AZD5305

Part A focused on establishing the maximum tolerated dose of AZD5305 monotherapy

- Advanced/metastatic ovarian, HER2-negative breast, pancreatic, or prostate cancer
- Loss of function mutation in ***BRCA1, BRCA2, PALB2, RAD51C*** **or** ***RAD51D****
- Up to one prior line of PARPi
- Platinum-sensitive or resistant/refractory permitted
- ECOG 0–2
- Hgb ≥9 g/dL



Primary endpoint

- Safety and tolerability

Other endpoints

- Pharmacokinetics
- PD in PBMCs and paired tumour samples
- Preliminary efficacy
- ctDNA analysis (baseline, longitudinal and at progression)

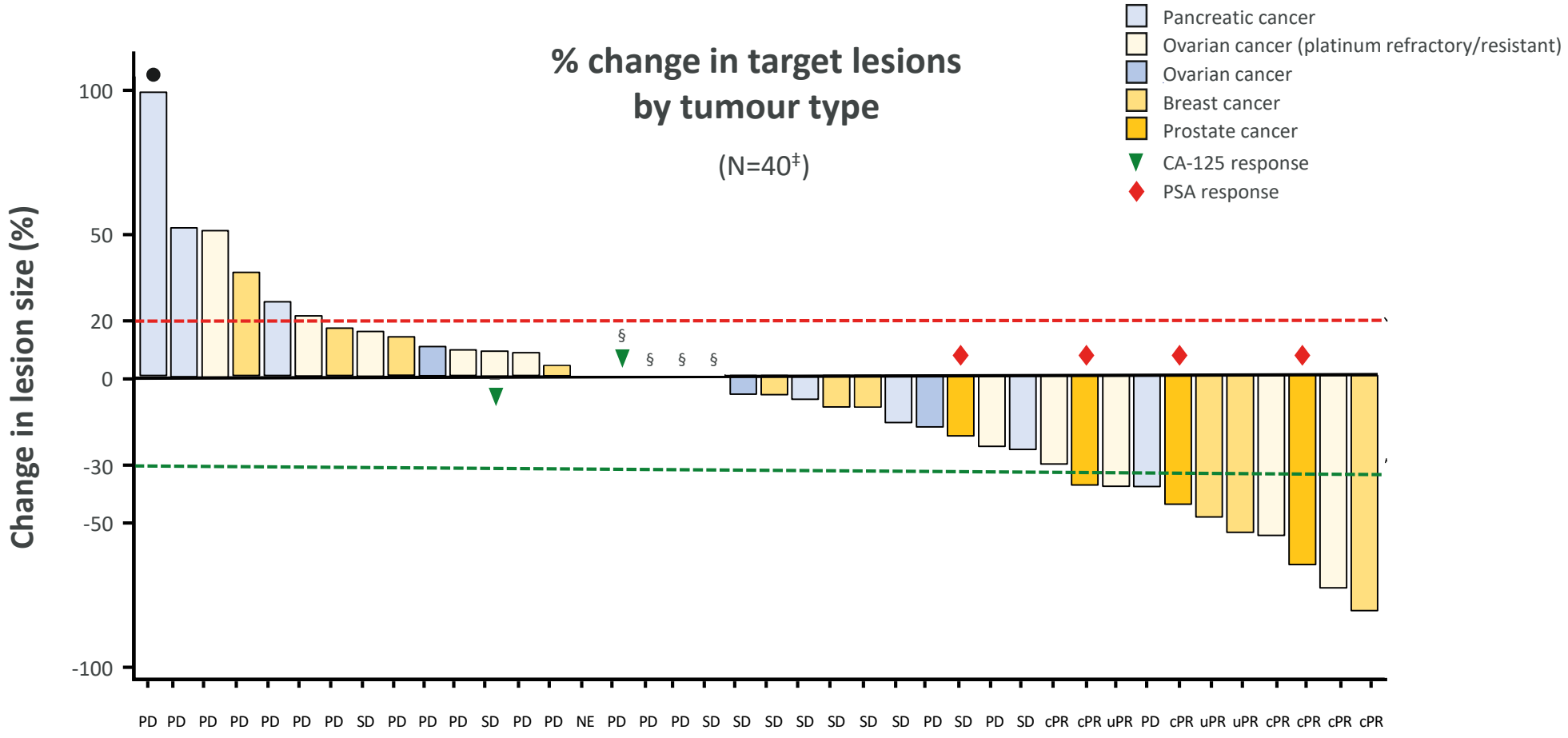
First presentation of data for this ongoing study. First patient dosed: 25 November 2020. DCO: 22 February 2022. Monotherapy dose escalation: 61 patients dosed from 10 mg to 140 mg QD

*Only blood or tissue local testing; retrospective tissue central confirmation

ANC=absolute neutrophil count; ctDNA=circulating tumour DNA; ECOG=Eastern Cooperative Oncology Group; HER2=human epidermal growth factor receptor 2; Hgb=haemoglobin; PARPi=poly(ADP-ribose) polymerase inhibitor; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamics

1. Yap TM, et al. Presented at AACR 2022. 8–13 April. New Orleans, Louisiana. Abstract #CT007; 2. PETRA. Available at: clinicaltrials.gov https://clinicaltrials.gov/ct2/show/NCT04644068 (Last accessed April 2022)

RECIST v1.1 responses were observed with AZD5305 across multiple tumour types*[1]



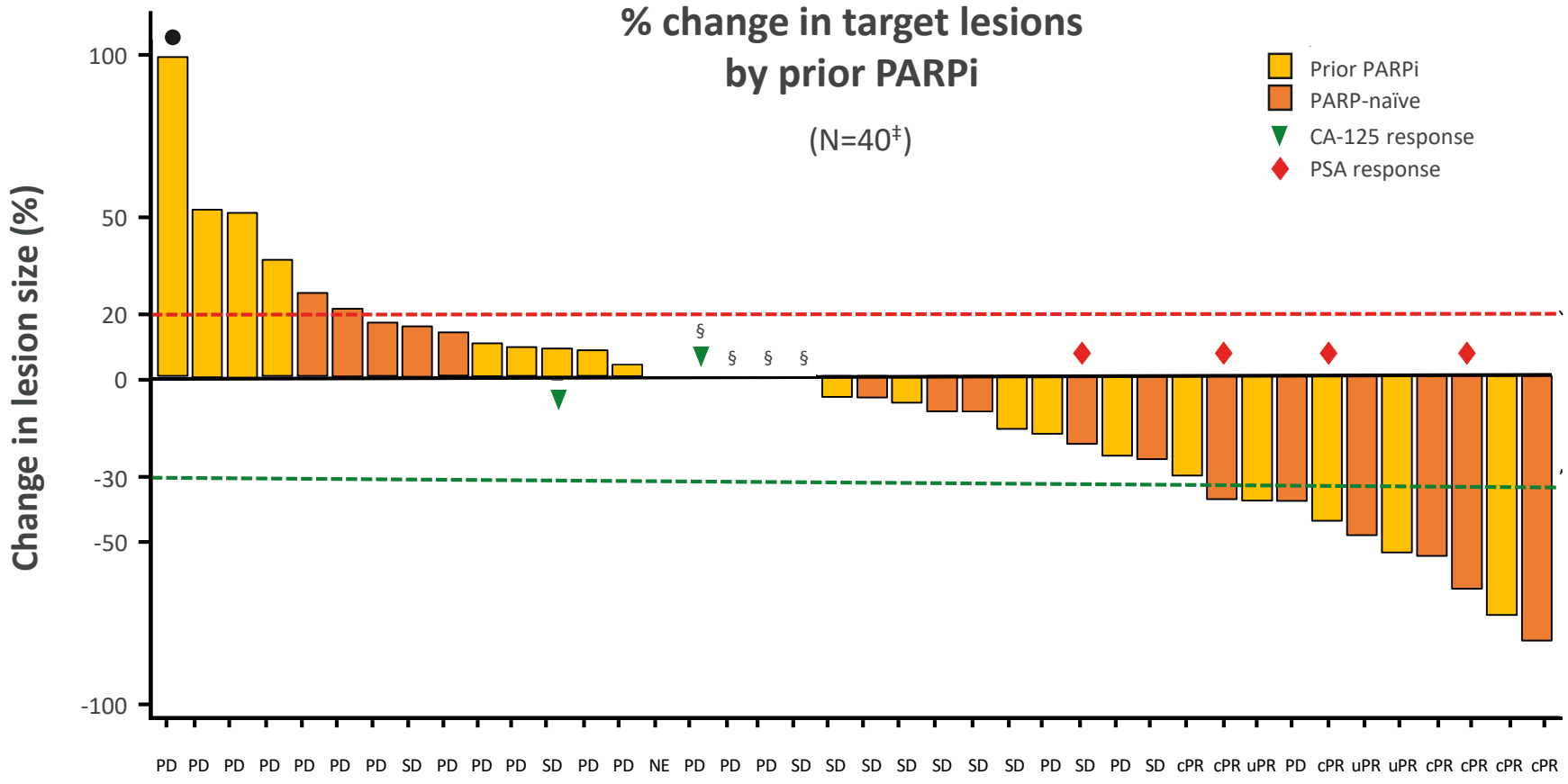
Note: Included patients pre-treated with PARPi and patients eligible independently of platinum sensitivity

*Of the 40 patients evaluable for RECIST v1.1†, 10 had partial responses (7 confirmed; 3 unconfirmed) and 11 reported stable disease. †n=6 pts were Not evaluable: n=5 did not have a follow up scan and n=1 had SD <7 weeks.

‡n=6 patients did not have a post baseline assessment include n=1 patient with an early death. §Patients with 0% change from baseline; percent change >100 was cut at 100 and marked with black dot.
CA-125=cancer antigen 125; (c)PR=(confirmed) partial response; eCRF=electronic case report form; NE=not evaluable; PD=progressive disease; PSA=protein-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease; (u)PR=(unconfirmed) partial response

1. Yap TM, et al. Presented at AACR 2022. 8–13 April. New Orleans, Louisiana. Abstract #CT007

RECIST v1.1 responses were observed with AZD5305 regardless of prior PARPi use*[1]



Note: Included patients pre-treated with PARPi and patients eligible independently of platinum sensitivity

*Of the 40 patients evaluable for RECIST v1.1†, 10 had partial responses (7 confirmed; 3 unconfirmed) and 11 reported stable disease. †n=6 pts were Not evaluable: n=5 did not have a follow up scan and n=1 had SD <7 weeks. ‡n=6 patients did not have a post baseline assessment include n=1 patient with an early death. §Patients with 0% change from baseline; percent change >100 was cut at 100 and marked with black dot.
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1. Yap TM, et al. Presented at AACR 2022. 8–13 April. New Orleans, Louisiana. Abstract #CT007

	Starting age surveillance	MX	MRI	RRM
ATM	30 y	40 y annually	30 y annually	Evidence insufficient Manage on FH basis
CHEK2	30y	40 y annually	30 y annually	Evidence insufficient Manage on FH basis
BARD1	40 y	>40 y annually	40 y annually	Evidence insufficient Manage on FH basis
RAD51C	40 y	>40 y annually	40 y annually	Evidence insufficient Manage on FH basis
Rad51D	40 y	>40 y annually	40 y annually	Evidence insufficient Manage on FH basis

NCCN Guidelines 2023

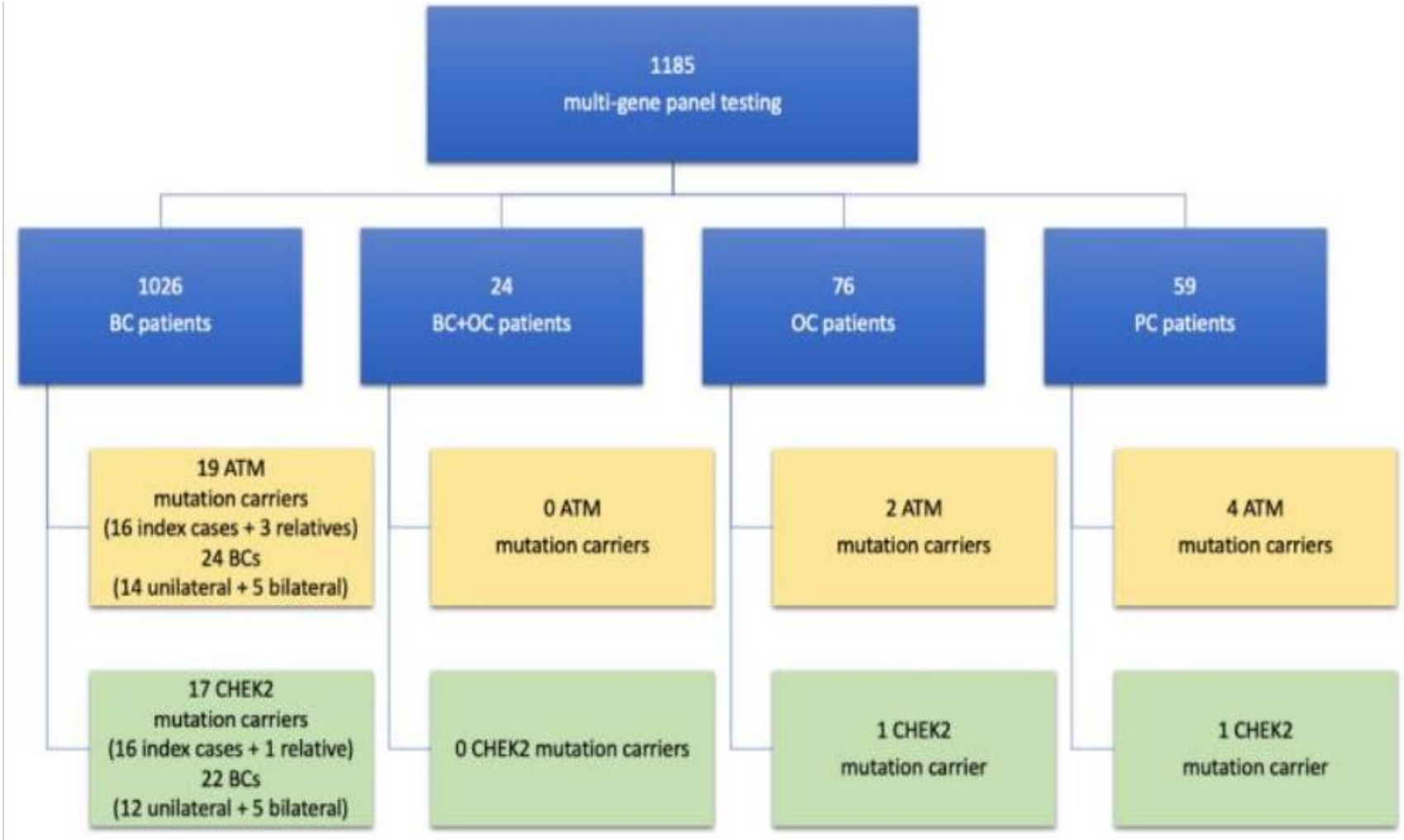
Table 2. Estimated Lifetime Benefits of MRI Screening Strategies With Annual Mammography From Age 40 to 74 Years Alone and With Annual MRI at Varying Start Ages for Modeled Women With *ATM*, *CHEK2*, and *PALB2* Pathogenic Variants

	Breast cancer mortality reduction, mean (range), %[a]			Life-years gained per 1000 women, mean (range)[a]			Breast cancer deaths averted per 1000 women, mean (range)[a]		
Start age	*ATM*	*CHEK2*	*PALB2*	*ATM*	*CHEK2*	*PALB2*	*ATM*	*CHEK2*	*PALB2*
Annual mammography at 40 y	38.5 (37.8-39.2)	38.4 (38.0-38.8)	36.4 (34.6-38.2)	291 (263-319)	370 (330-409)	621 (559-684)	13.3 (9.0-17.6)	17.4 (11.6-23.1)	29.7 (22.0-37.4)
Plus MRI at 40 y	53.6 (52.9-54.3)	53.6 (53.3-53.9)	52.3 (51.4-53.1)	420 (388-452)	533 (489-577)	921 (876-967)	18.4 (12.5-24.4)	24.2 (16.4-32.1)	42.4 (32.7-52.2)
Plus MRI at 35 y	57.6 (57.2-58.0)	57.0 (56.3-57.7)	54.4 (54.2-54.7)	473 (447-498)	591 (555-627)	992 (959-1025)	19.7 (13.7-25.7)	25.6 (17.7-33.5)	44.0 (34.4-53.7)
Plus MRI at 30 y	59.5 (58.5-60.4)	58.4 (57.2-59.6)	55.4 (55.3-55.4)	501 (478-523)	620 (587-652)	1025 (998-1051)	20.3 (14.3-26.2)	26.2 (18.3-34.1)	44.7 (35.2-54.3)
Plus MRI at 25 y	60.2 (58.9-61.2)	58.9 (57.5-60.3)	55.7 (55.5-55.8)	510 (489-531)	630 (599-661)	1037 (1013-1061)	20.5 (14.5-26.4)	26.4 (18.5-34.2)	45.0 (35.4-54.5)

Abbreviation: MRI, magnetic resonance imaging.

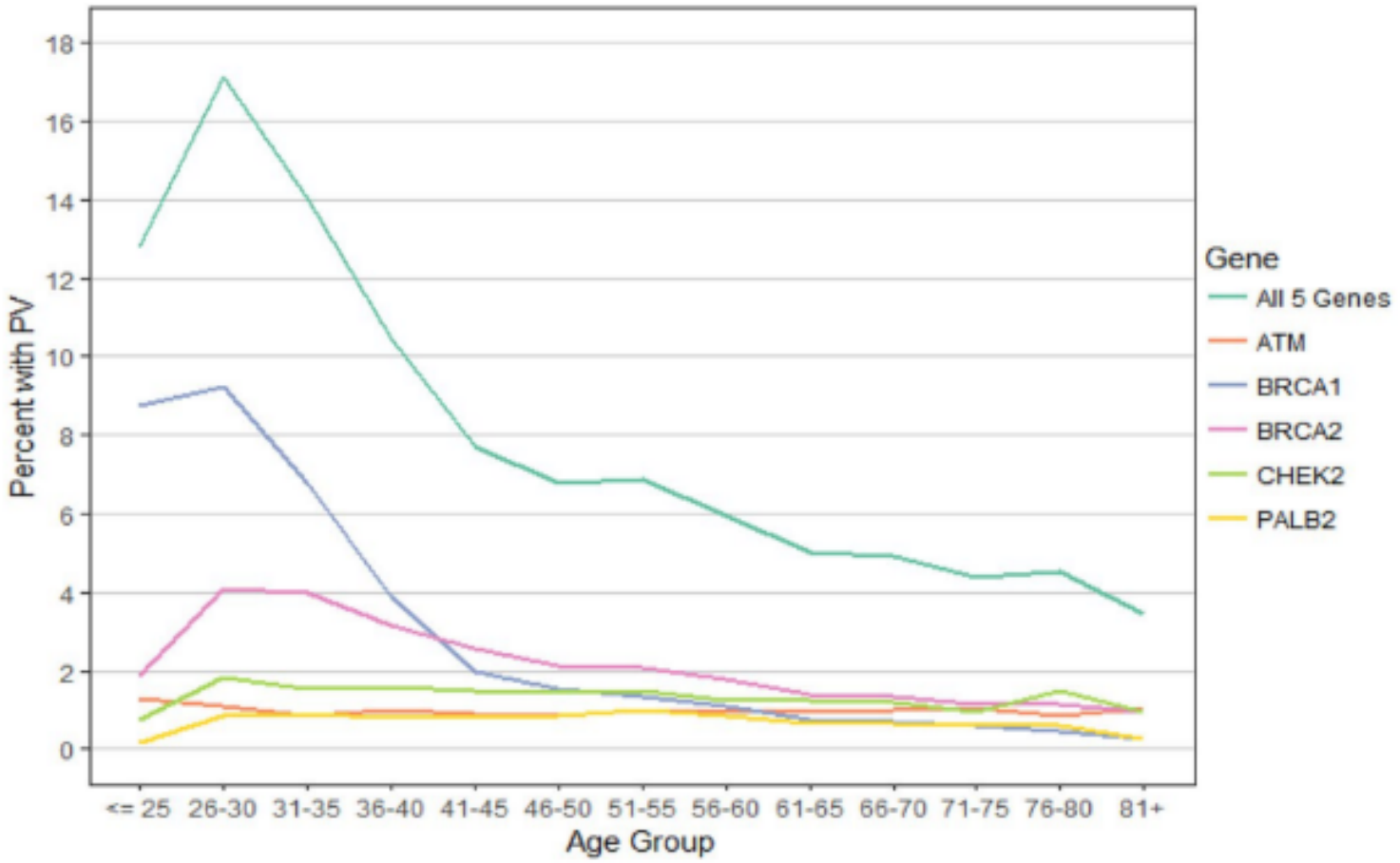
[a] Results are shown as mean values of cumulative lifetime outcomes per 1000 women screened across Model E (Erasmus Medical Center, Rotterdam, the Netherlands) and Model W-H (University of Wisconsin-Madison, Madison; Harvard Medical School, Boston, Massachusetts).

Lowry KP et al., Jama Oncol 2022



Toss A., Genes 2021

The association between age at breast cancer diagnosis and prevalence of pathogenic variants



Daly MB et al, BRCT 2023

Association between PV/BC genes and BC risk

Breast Cancer–Predisposition Gene[1,2,7]	Case Patients (N=32,247)	Controls (N=32,544)	Odds Ratio (95% CI)†	P Value
	no. with pathogenic variant (%)			
ATM	253 (0.78)	134 (0.41)	1.82 (1.46–2.27)	<0.001
BARD1	49 (0.15)	35 (0.11)	1.37 (0.87–2.16)	0.18
BRCA1	275 (0.85)	37 (0.11)	7.62 (5.33–11.27)	<0.001
BRCA2	417 (1.29)	78 (0.24)	5.23 (4.09–6.77)	<0.001
CDH1	17 (0.05)	6 (0.02)	2.50 (1.01–7.07)	0.06
CHEK2	349 (1.08)	138 (0.42)	2.47 (2.02–3.05)	<0.001
NF1‡	19 (0.06)	11 (0.03)	1.93 (0.91–4.31)	0.09
PALB2	148 (0.46)	38 (0.12)	3.83 (2.68–5.63)	<0.001
PTEN	8 (0.02)	3 (0.01)	NA	NA
RAD51C	41 (0.13)	35 (0.11)	1.20 (0.75–1.93)	0.44
RAD51D	26 (0.08)	14 (0.04)	1.72 (0.88–3.51)	0.12
TP53‡	19 (0.06)	2 (0.01)	NA	NA
Total	1621 (5.03)	531 (1.63)	—	—

C. Hu, NEJM, 2021

Is the age>65 years associated or not with hereditary BC?

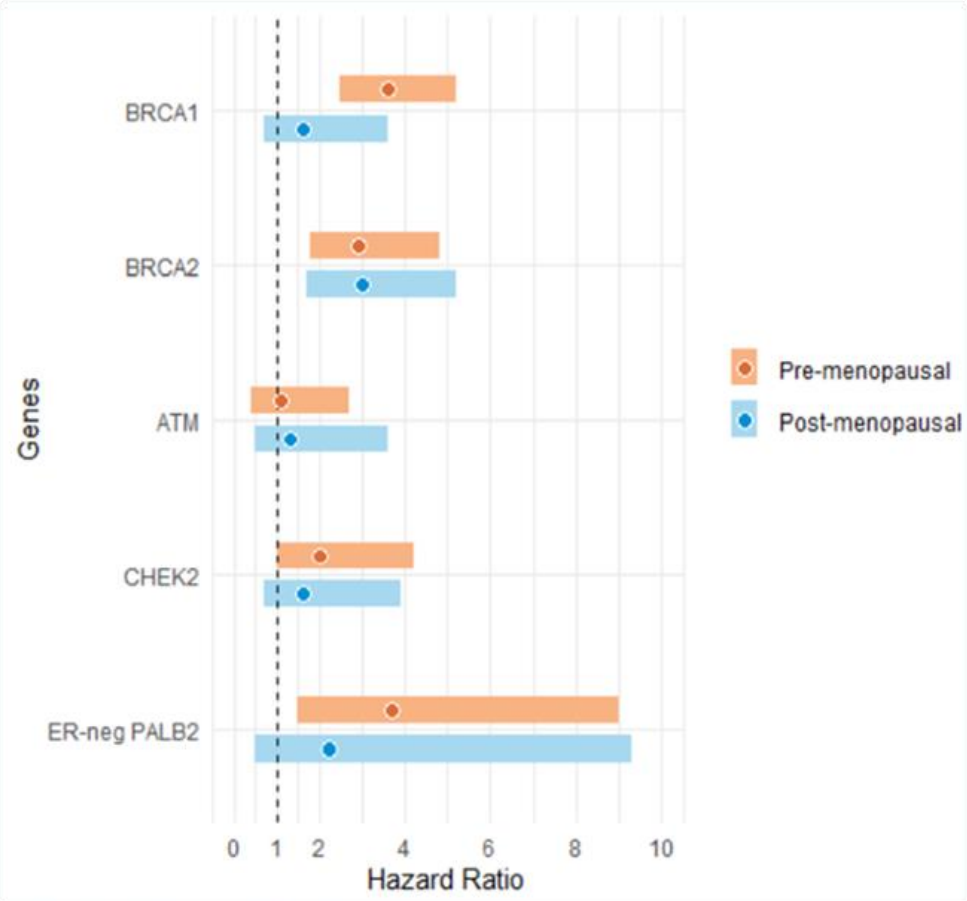
Women with BC diagnosed > 65 yrs with no other significant risk factors are not recommended by NCCN to receive genetic test on the basis of a presumed low yield (<2.5% probability of HP-PV)

	ER-Positive (n = 9,128)			ER-Negative (n = 1,488)		
Gene	**PV, No. (%)**	**OR (95% CI)**	***P***	**PV, No. (%)**	**OR (95% CI)**	***P***
Established Breast Cancer Predisposition Genes						
ATM	52 (0.57)	1.38 (0.91 to 2.08)	.130	7 (0.47)	0.83 (0.28 to 1.96)	.698
BARD1[a]	4 (0.04)	0.62 (0.17 to 1.94)	.433	4 (0.27)	4.15 (1.10 to 13.10)	.020
BRCA1	12 (0.13)	1.33 (0.54 to 3.37)	.531	14 (0.94)	9.69 (4.01 to 24.24)	5.14×10^{-7}
BRCA2	51 (0.56)	2.12 (1.34 to 3.41)	.002	27 (1.81)	7.15 (4.15 to 12.23)	7.34×10^{-13}
CDH1	0 (0.00)	NA	NA	0 (0.00)	NA	NA
CHEK2	92 (1.01)	2.30 (1.60 to 3.34)	9.23×10^{-6}	9 (0.60)	1.53 (0.67 to 3.09)	.271
NF1[b]	1 (0.01)	NA	NA	2 (0.13)	NA	NA
PALB2	28 (0.31)	2.66 (1.35 to 5.55)	.006	10 (0.67)	7.10 (2.82 to 17.27)	1.72×10^{-5}
PTEN	1 (0.01)	NA	NA	0 (0.00)	NA	NA
RAD51C	9 (0.10)	1.02 (0.41 to 2.44)	.973	3 (0.20)	NA	NA
RAD51D[a]	6 (0.07)	1.62 (0.47 to 5.81)	.436	4 (0.27)	6.75 (1.62 to 26.26)	.005
TP53[b]	0 (0.00)	NA	NA	1 (0.07)	NA	NA
Total	256 (2.80)			78 (5.24)		

In women >65yrs PVs in established BC predisposition genes were identified in 3.18% of 13,762 women with BC and 1.48% of 12,945 age-matched unaffected women

Boddicker et al JCO 2021

Contralateral Breast Cancer Risk by **Menopausal Status** at First Breast Ca Diagnosis



Adjusted Hazard Ratios

	10-year Cumulative Incidence of CBC*	
	Pre-menopausal	**Post-menopausal**
Non-carriers	5.8%	3.7%
BRCA1	33%	11%
BRCA2	27%	9.5%
ATM	2.9%	4.6%
CHEK2	13%	4.3%

*: Unadjusted analysis

Yadav S, JCO 2023

PERSONALISED SCREENING: when it is needed

Increased breast density: RR 1.77 to 2.45

Personal history of DCIS or LCIS/AH

Exposure to ionizing radiation (especially during puberty or young adulthood): risk starting 10 yrs after exposure and persisting lifelong; 6-fold increase overall

Positive family history

High risk women:

Carriers of germline mutation in BC predisposition genes (*BRCA1, BRCA2, PALB2, TP53, PTEN, STK11,...*);

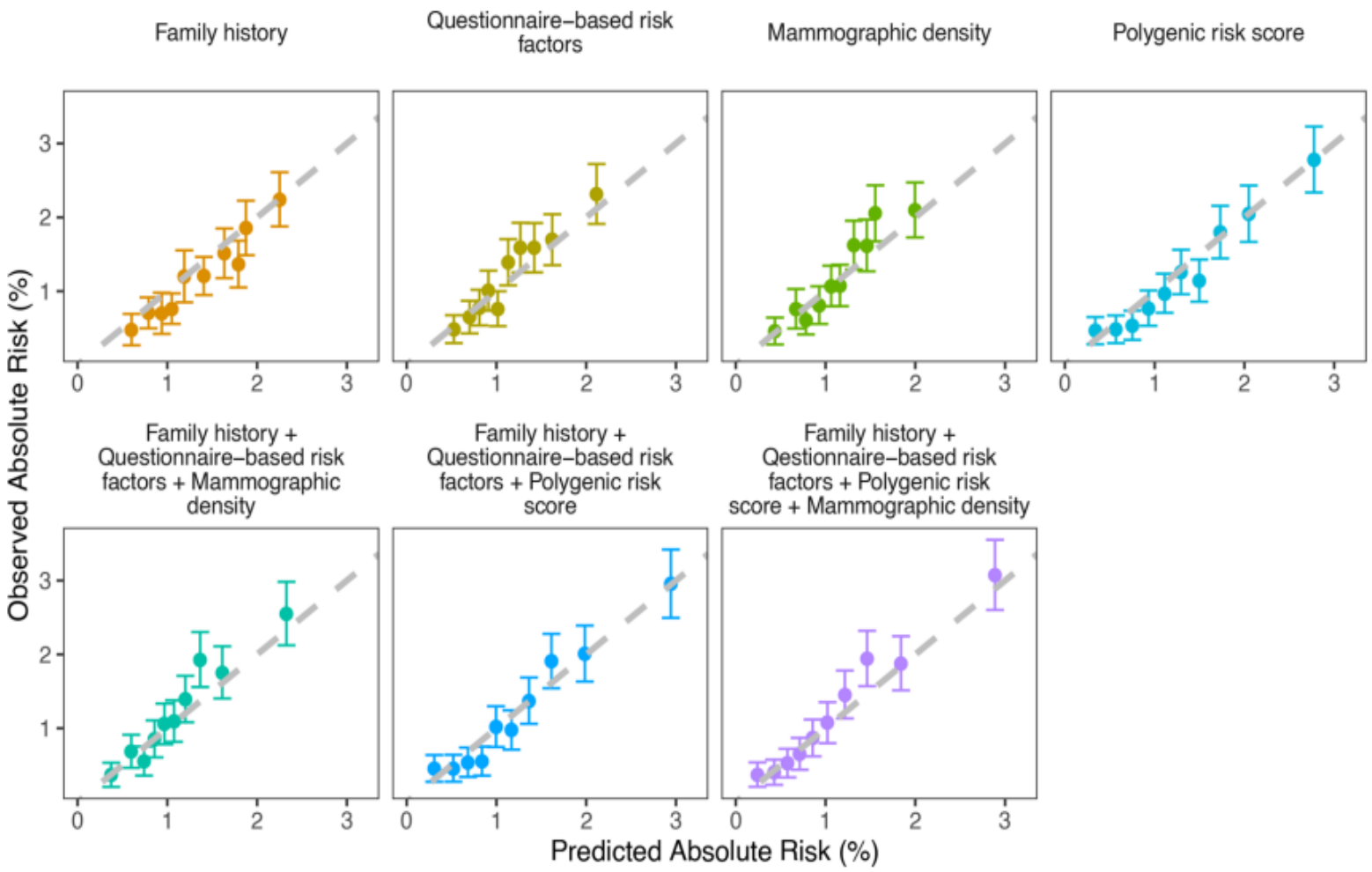
PRS313 score >90%:lifetime risk 32.6%

BC risk greater than 20–30% lifetime as estimated by risk prediction models.

Predictive models' comparison

Factor	Gail	Claus	BRCAPRO	IBIS	Current BOADICEA	Extended BOADICEA[h]
Family history	YES (descriptive)	YES	YES	YES	YES	YES
BRCA1/2	NO	NO	YES	YES	YES	YES
Common low-risk alleles	NO[b]	NO	NO	NO	YES[c]	YES
Intermediate risk mutations (*CHEK2*, *PALB2*, *ATM* etc)	NO	NO	NO	NO	NO	YES
Residual non-*BRCA1/2* familial aggregation	NO	NO	NO	Dominant	YES	YES
BRCA1/2-pathology associations	NO	NO	YES[e]	NO	YES	YES
BRCA1/2 risk modification	NO	NO	NO	NO	YES	YES
Variants of uncertain significance	NO	NO	NO	NO	NO	YES
Predicting ER-specific risks	NO	NO	NO	NO	NO	YES
Mammographic Density (MD)	NO	NO	NO	NO	NO	YES
Hormonal, Lifestyle, Reproductive	YES	NO	NO	YES Same effect on BRCA1/2	NO	YES
Other cancers (non-BC or OvC)	NO	NO	YES	NO	YES	YES
Predicting second cancer risks (CBC,	NO	NO	NO	NO	YES	YES

Lee et al Genetics in Medicine, 2019



Yang X et al., J Med Genet 2022

PRS may facilitate personalization of BC risk among carriers of moderate risk PVs

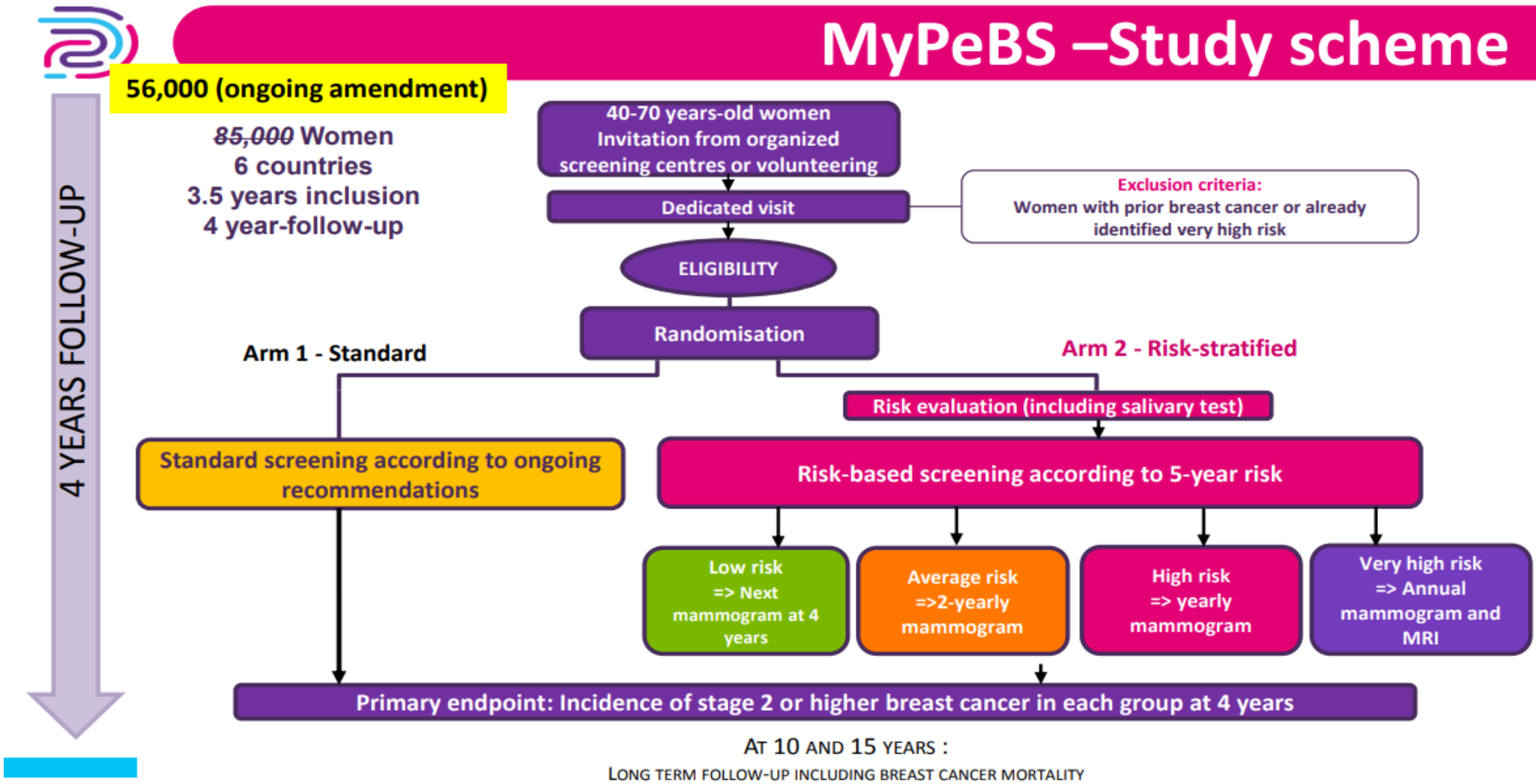
- PRS = polygenic risk score (measure of the aggregate impact of SNPs)
- Substantial proportion of patients with *ATM* and *CHEK2* PVs may have <20% lifetime BC risk
  - Gao et al.: 30.3% pts w *CHEK2* PV and 47.5% w *ATM* PV would be reclassified by PRS as having lifetime risk <20%

TABLE 3. Lifetime Absolute BC Risk (by age 80 years) of BC for Different Pathogenic Variant Carriers With Respect to Different PRS Percentile and BC Family History Status

Lifetime Absolute Risk (95% CI)	No Family History				Family History of BC (First-Degree Relative)			
	10th Percentile PRS	Median PRS	Mean PRS	90th Percentile PRS	10th Percentile PRS	Median PRS	Mean PRS	90th% PRS
Noncarrier	6.7 (6.6 to 6.9)	11.1 (11.1 to 11.2)	12.1 (12.0 to 12.1)	18.3 (17.9 to 18.7)	9.1 (8.6 to 9.6)	14.8 (14.2 to 15.5)	15.9 (15.3 to 16.6)	23.9 (22.9 to 25.0)
BRCA1 carrier	36.1 (26.4 to 48.5)	41.2 (32.6 to 52.0)	41.4 (32.8 to 52.2)	46.9 (33.9 to 62.7)	45.4 (33.9 to 59.2)	51.1 (41.2 to 62.7)	51.3 (41.4 to 62.6)	57.3 (42.8 to 72.9)
BRCA2 carrier	43.8 (33.6 to 56.3)	49.3 (40.7 to 59.4)	49.5 (41.0 to 59.5)	55.3 (42.0 to 70.1)	53.9 (42.4 to 66.9)	59.8 (50.7 to 69.9)	59.9 (50.8 to 69.8)	65.9 (51.8 to 79.3)
ATM carrier	12.8 (10.3 to 15.9)	20.5 (16.7 to 25.2)	21.9 (18.0 to 26.6)	32.3 (26.8 to 38.8)	17.0 (13.7 to 21.1)	26.7 (21.9 to 32.5)	28.2 (23.3 to 34.0)	40.9 (34.2 to 48.5)
CHEK2 carrier	15.2 (12.6 to 18.2)	24.1 (20.3 to 28.5)	25.5 (21.6 to 30.0)	37.3 (32.0 to 43.4)	20.0 (16.7 to 24.0)	31.1 (26.3 to 36.6)	32.6 (27.8 to 38.0)	46.6 (40.3 to 53.4)
PALB2 carrier	21.5 (15.4 to 29.7)	33.2 (24.2 to 44.2)	34.6 (25.7 to 45.3)	49.2 (37.6 to 62.1)	27.9 (20.1 to 38.0)	41.9 (31.3 to 54.3)	43.1 (32.7 to 54.7)	59.5 (46.8 to 72.0)

Gallagher et al., *JCO Precis Oncol* 2021, PMID: 34322652; Gao et al., *J Clin Oncol* 2021, PMID: 34101481; Muranen et al., *Genet Med* 2017, PMID: 27711073; Borde et al., *J Natl Cancer Inst* 2021, PMID: 33372680

MyPeBS –Study scheme



AT 10 AND 15 YEARS :

LONG TERM FOLLOW-UP INCLUDING BREAST CANCER MORTALITY

Median and mean 5 year risk by stratification level

5 year risk of invasive BC

Risk categories	N (%)	Median score (range)	Mean score (sd)
Low risk (<1%)	2290 (36.41%)	0.67 (0.10; 0.99)	0.64(0.22)
Average risk (>=1% and <1.67%)	1814 (28.84%)	1.28 (1.00; 1.66)	1.29(0.19)
High risk (>=1.67% and <6%)	2108 (33.52%)	2.40 (1.67; 5.99)	2.71(0.97)
Very high risk (>=6%)	77 (1.22%)	7.30 (6.00; 18.71)	7.91(1.96)

Real time genotyping: feasibility

1. Saliva sampling

2. DNA extraction

2.5% excluded
(DNA concentration or integrity)

3. Genotyping + PRS313 assessment

1.2% genotyping failure

4. Global risk assessment

96.3% success*

5. Risk feedback

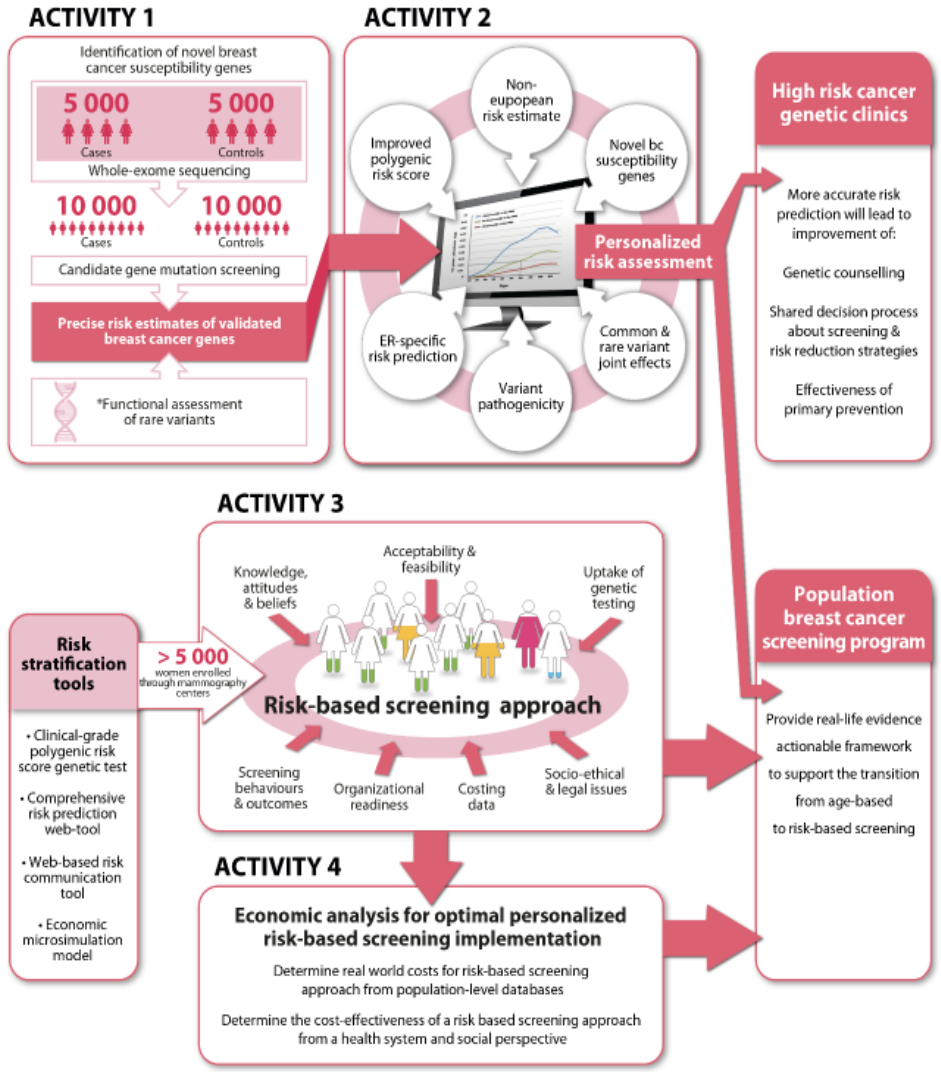
Mean turnover time from saliva sampling to risk result available was 11 weeks despite the COVID pandemic (currently 7 weeks).

*Where PRS313 is not available, risk is estimated based on clinical parameters only

Delaloge et al, 135P

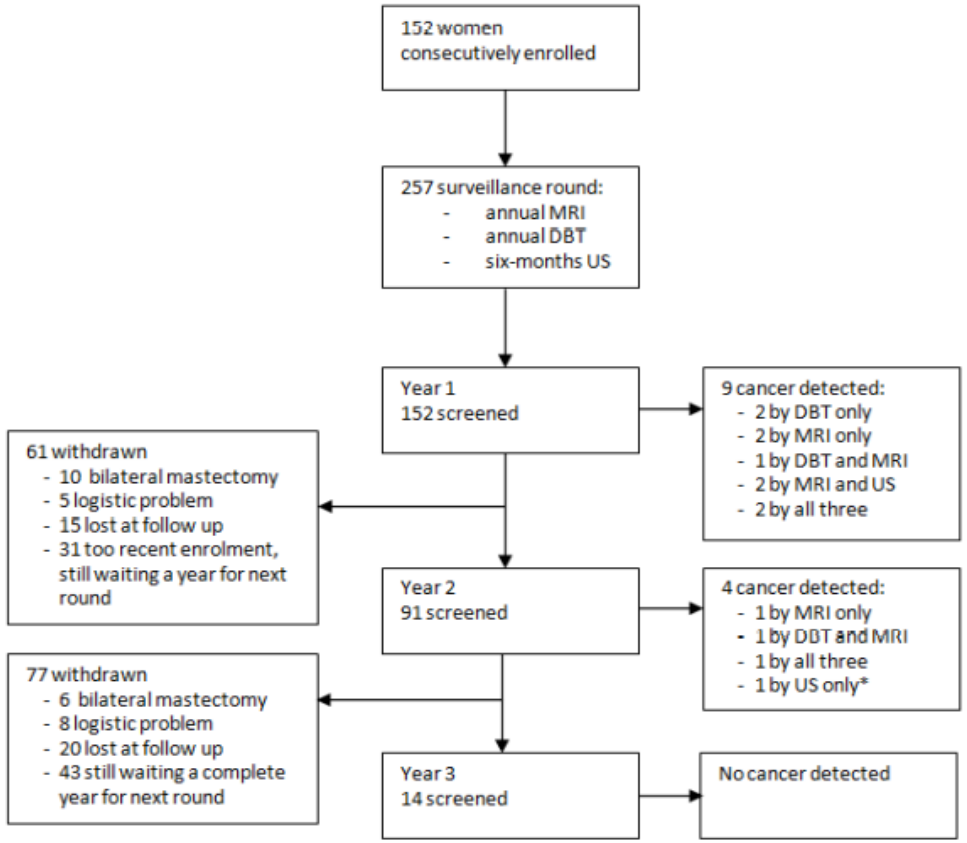
Perspective I&I Project

- This Canadian project is comprised of four connec
- 1. Identification and validation of **novel moderate susceptibility genes** through a well-powered whol case-control study, in order to develop a more **cor test**.
- 2. Improvement, validation and adaptation of a **co web-tool suitable to the Canadian context.**
- 3. Development and piloting of a socio-ethical frar **implementation of a personalized risk-based app screening at the population level.**
- 4. **Economic analysis** to optimize personalized risk implementation



Brooks JD et al, J Pers Med. 2021

Digital Breast Tomosynthesis vs. MRI vs. US



BRCA1	BRCA2	VUS	ATM	BRCAPRO>30%	CHEK2	MSH2	MUTYH	PALB2	TP53
63	62	7	5	3	4	1	2	2	1

Bettelli L et al., BJR submitted

	Sensitivity	*p* value	Specificity	*p* value	PPV	*p* value	NPV	*p* value
Digital breast tomosynthesis								
No/total No.	7/12	0.453*	243/245	0.0075	7/9	0.1007	243/248	0.2842
Rate, %	58.3		99.9		77.8		98	
95% CI	27.7 - 84.8		97.1 - 99.9		40.0 – 97.2		95.4 – 99.3	
Ultrasound								
No/total No.	5/12	0.0625*	237/245	0.2059	5/13	0.6863	237/244	0.1040
Rate, %	41.7		96.7		38.5		97.1	
95% CI	15.2 – 72.3		93.7 – 98.6		13.9 - 68.4		94.2 – 98.8	
Magnetic Resonance Imaging								
No/total No.	10/12	reference	233/245	reference	10/22	reference	233/235	reference
Rate, %	83.3		95.1		45.5		99.1	
95% CI	51.6 – 97.9		91.6 – 97.4		24.4 – 67.8		97 – 99.9	
Digital breast tomosynthesis and Ultrasound**								
No/total No.	9/12	1*	235/245	0.5637	9/19	0.9025	235/238	0.6633
Rate, %	75		95.9		47.4		98.7	
95% CI	42.8 – 94.5		92.6 – 98		24.4 – 71.1		96.4 – 99.7	
Digital breast tomosynthesis and Magnetic Resonance Imaging**								
No/total No.	12/12	0.5*	231/245	0.1573	12/26	0.9614	231/231	0.0869
Rate, %	100		94.3		46.2		100	
95% CI	73.5 – 100		90.6 – 96.8		26.6 – 66.6		98.4 – 100b	

Bettelli L et al., BJR submitted

Conclusions

- Carriers of high penetrance genes need surveillance with MRI starting 20-25 years
- Risk reducing mastectomy should be offered in p53, PTEN and STK11 carriers. For PALB2 and CDH1 should be evaluated according to family history
- P53 BC are mostly HER2 positive and HR+
- CDK4/6 inhibitors are less effective. Ruxolitinib (STAT1/2 inhibitor) is effective in p53 GBM
- The evidence level for MRI in PJS is low
- PARPi are equally effective in gBRCA,sBRCA e gPALB2
- New PARPi (Saruparib) are less toxic and more effective in HRR mutated
- No indication for risk reducing mastectomy in moderate genes
- TNBC PALB2 premenopausal patients have 4 fold the risk of CBC. Also CHEK2 have a double risk of CBC
- PRS could provide a personalized screening