Using genomics to identify new causes of cancer: a global context

Paul Brennan

International Agency for Research on Cancer
Lyon, France

About 40% of cancers can be explained by known risk factors

Parkin DM et al, BJC 2011

Many causes of cancer remain to be discovered

International Agency for Research on Cancer

World Health Organization

WCRF third report

WCRF third report

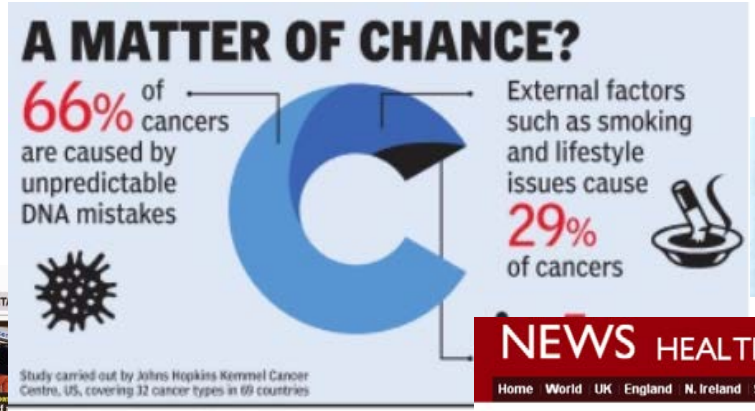
Around 42% of all cancers are preventable

WCRF third report

Around 42% of all cancers are preventable...
....based on current knowledge

What about the other 60%?

What about the other 60%?



International Agency

World Health Organization

What about the other 60%?

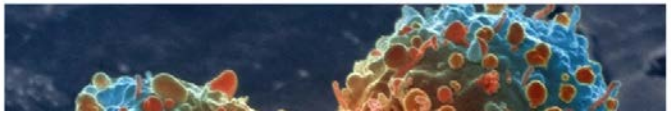
Its not chance!

Most cancer types 'just bad luck'

COMMENTS (868)

By James Gallagher

Health editor, BBC News website



International Agency

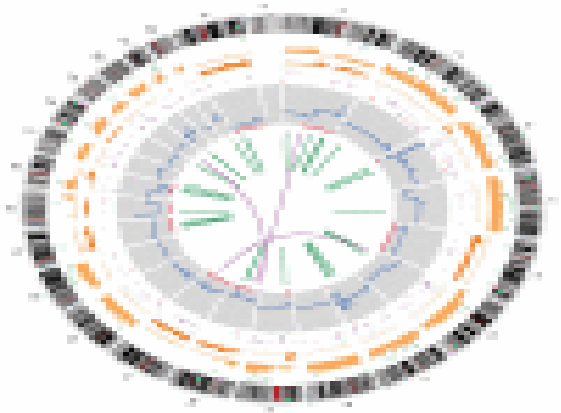
World Health Organization

Large international differences cannot be chance

Cancer site	Low incidence region	Incidence rate/100.000 (mortality)	High incidence region	Incidence rate/100.000 (mortality)
Prostate	Vietnam	3.2 (1.8)	Ireland	126 (17.9)
Brain	Singapore	1.8 (1.3)	US	6.3 (3.6)
Testes	South Korea	0.7 (0.1)	Norway	12.1 (0.2)
NHL	Vietnam	1.7 (1.2)	US	16.3 (4.0)
Kidney	Thailand	1.7 (1.0)	Czech Rep	23.6 (8.3)
Pancreas	India	1.1 (1.0)	Japan	10.0 (9.0)
Colorectal	Gambia	2.2 (2.0)	Japan	41 (15.2)

How can genomics reveal new causes of cancer?

1. The cancer genome
- mutation signatures



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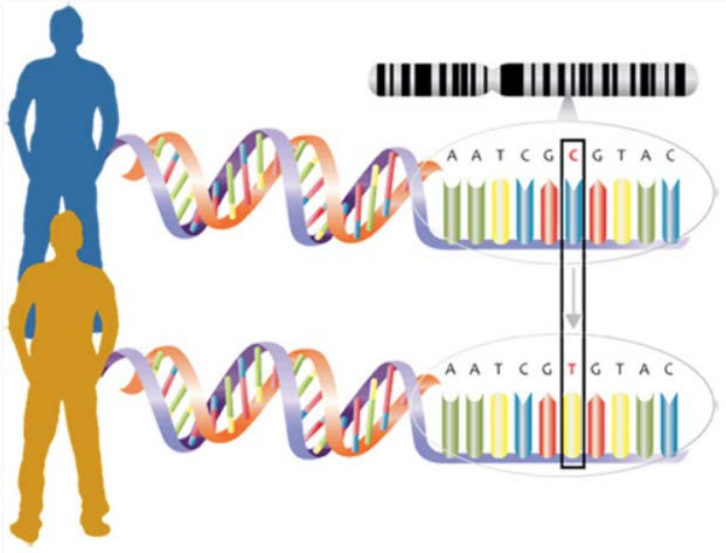
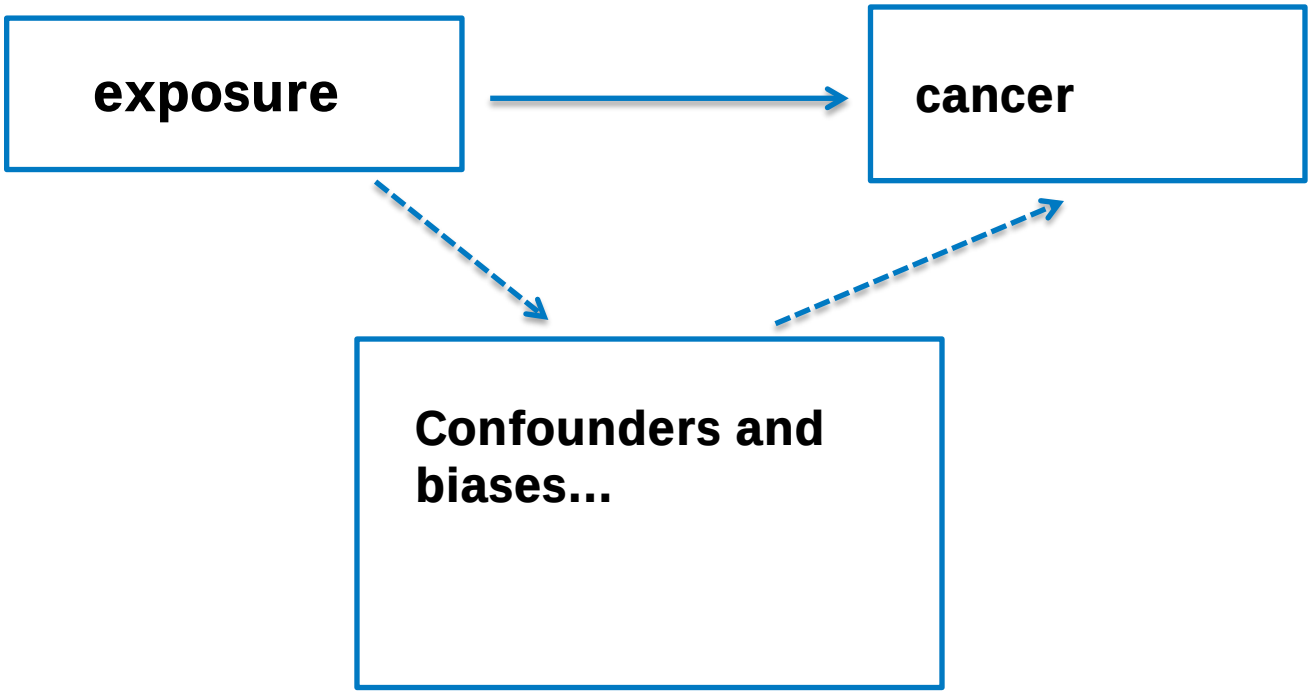
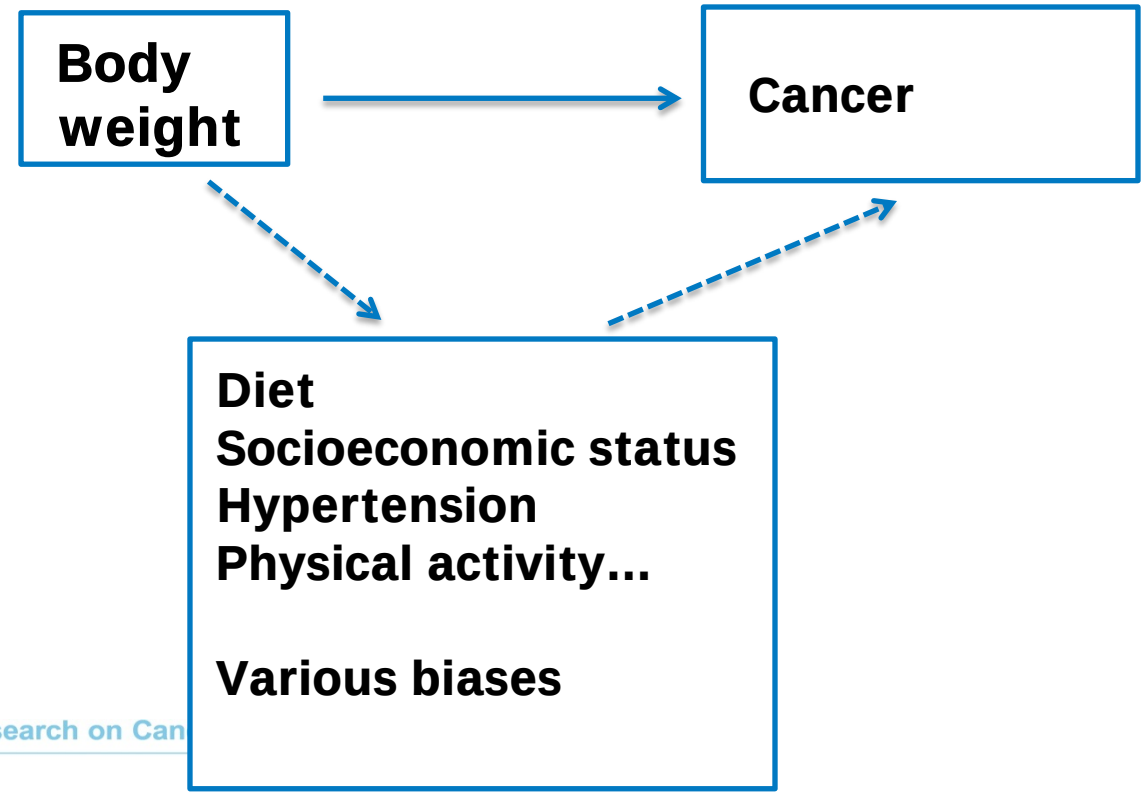
2. Our own germline variation
- Mendelian randomization



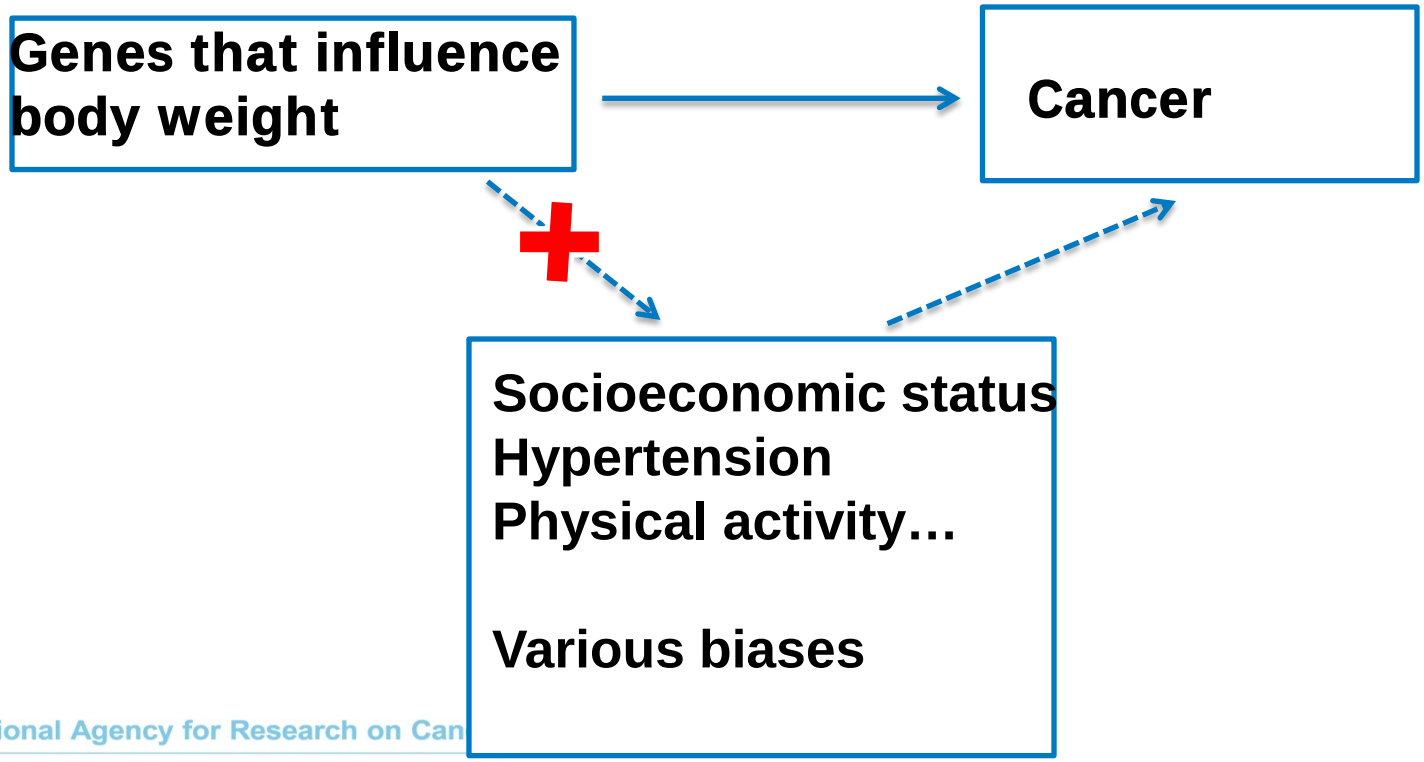
How epidemiology works



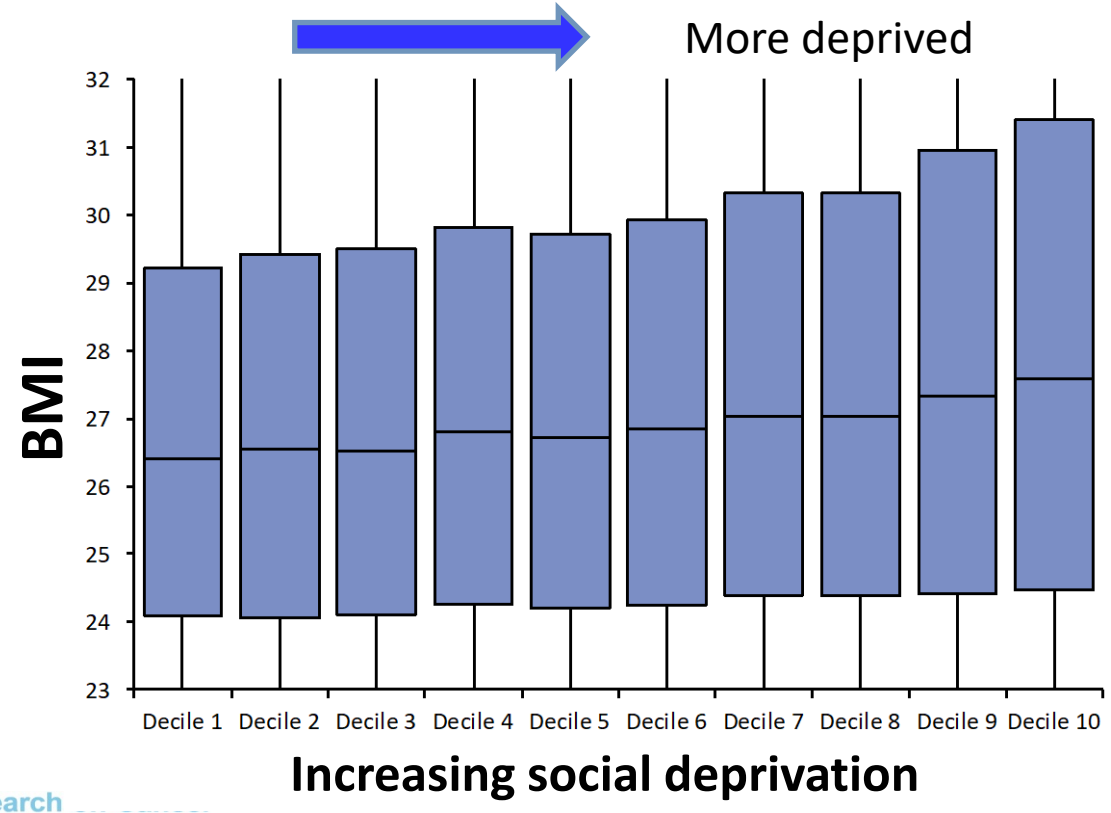
How epidemiology works



Mendelian randomization :
Use genes for an exposure/ not the exposure itself



Social deprivation and BMI among 500,000 UK adults



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UK Biobank

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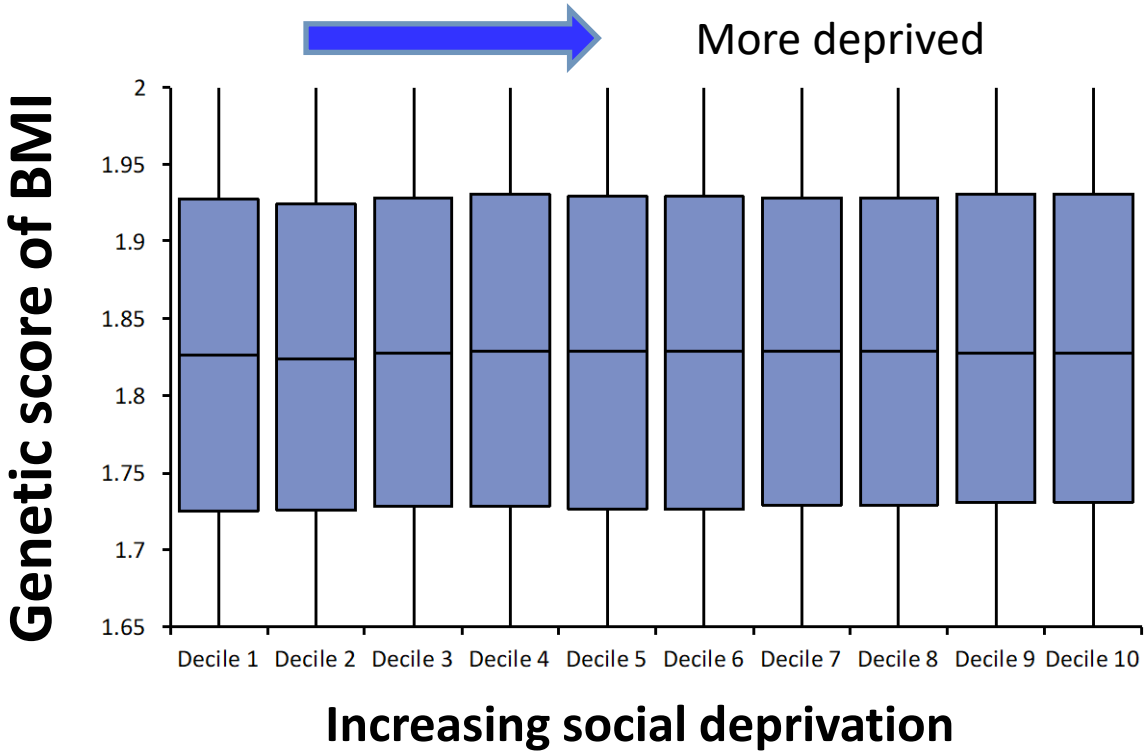

International Agency for Research on Cancer

World Health Organization

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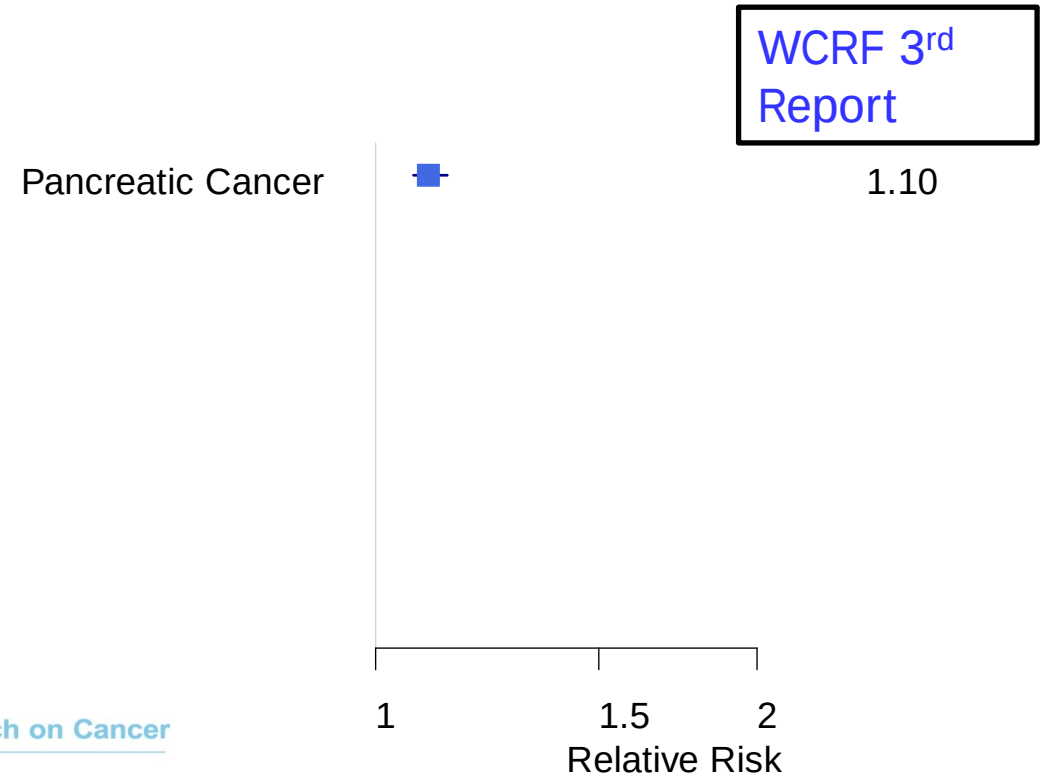
Effect of 5 BMI unit increase on cancer risk

WCRF third report v Mendelian randomization analysis



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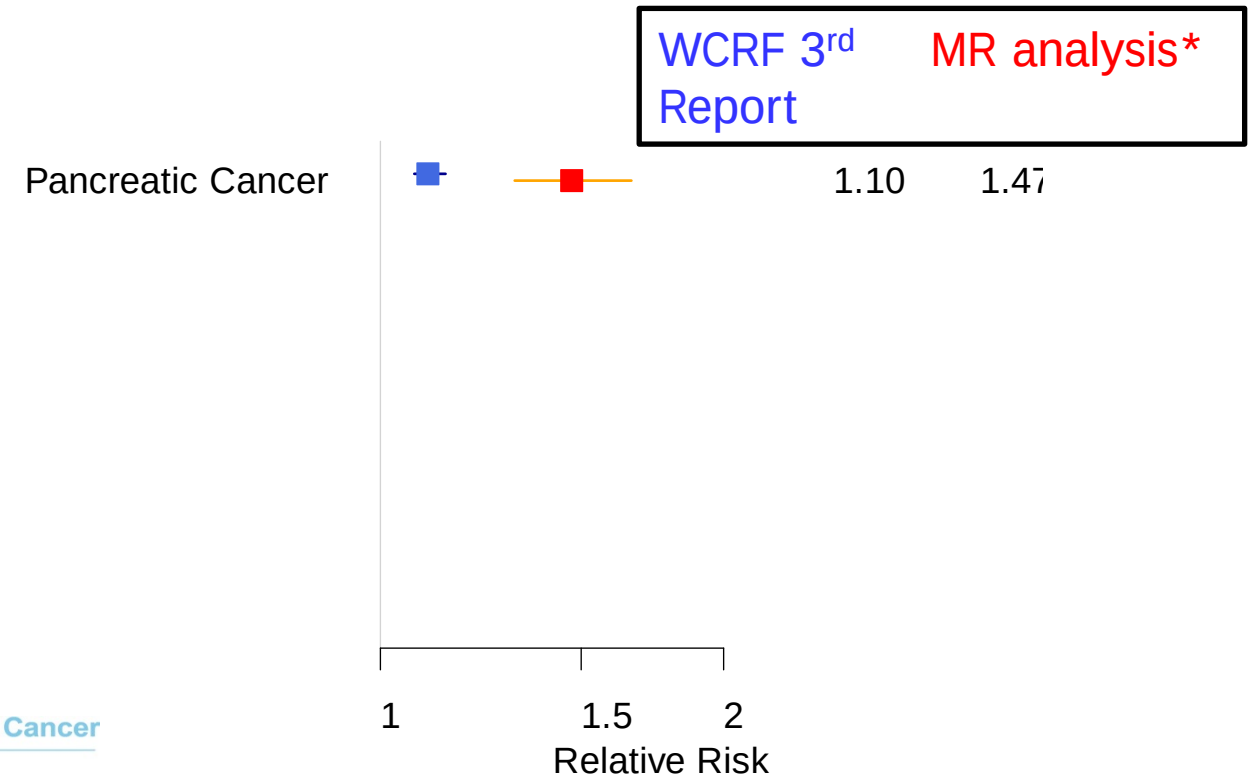

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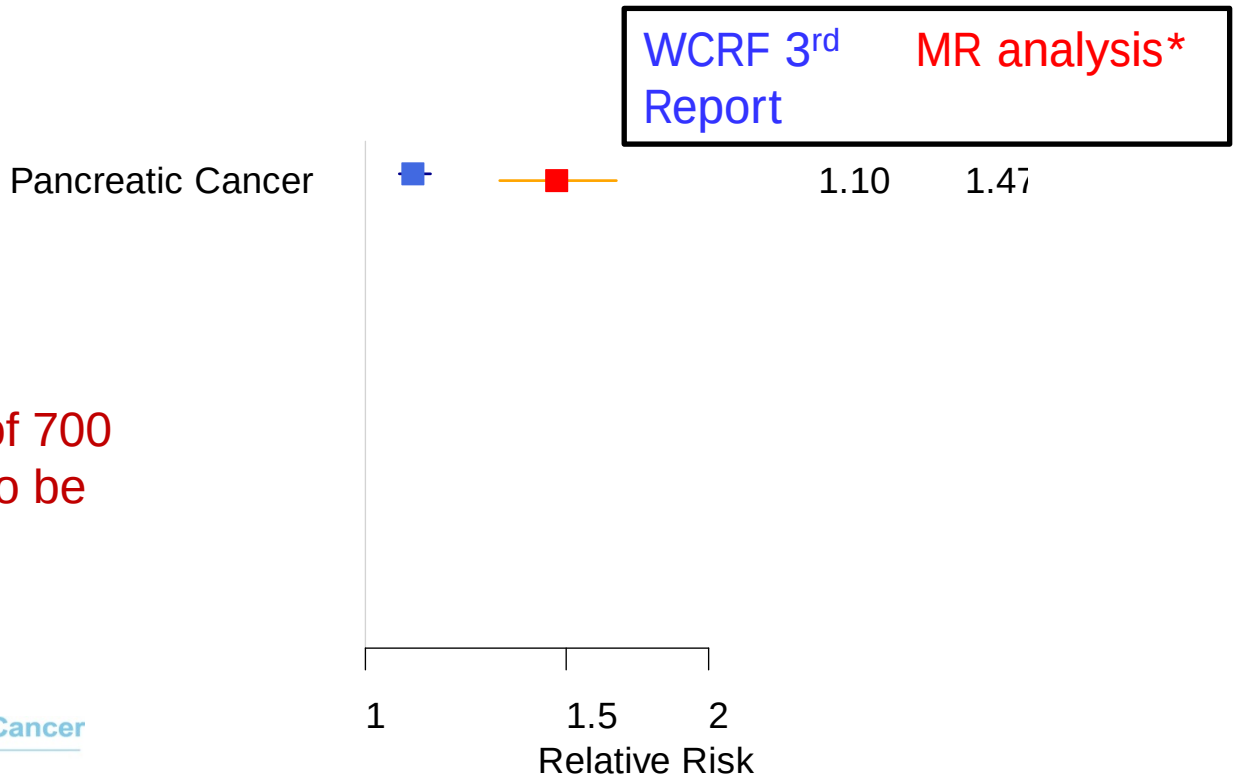
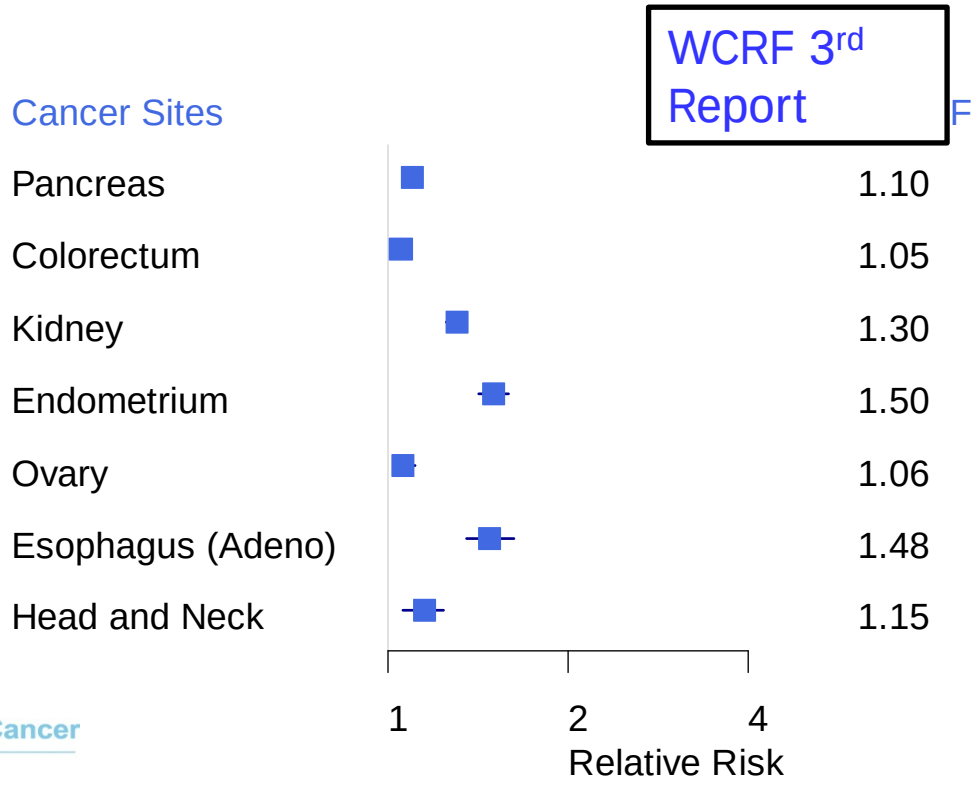


*Weighted measure of 700 gene variants found to be associated with BMI

Effect of 5 BMI unit increase on cancer risk

WCRF third report v Mendelian randomization analysis



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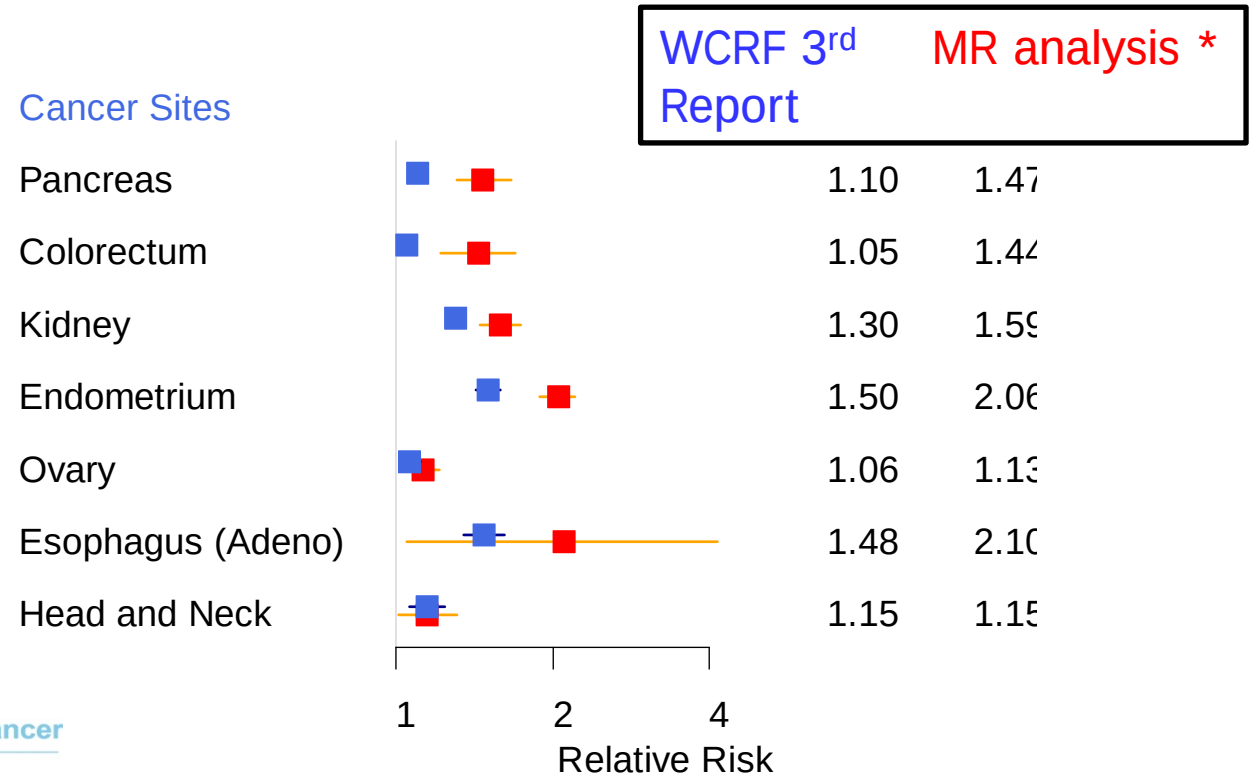

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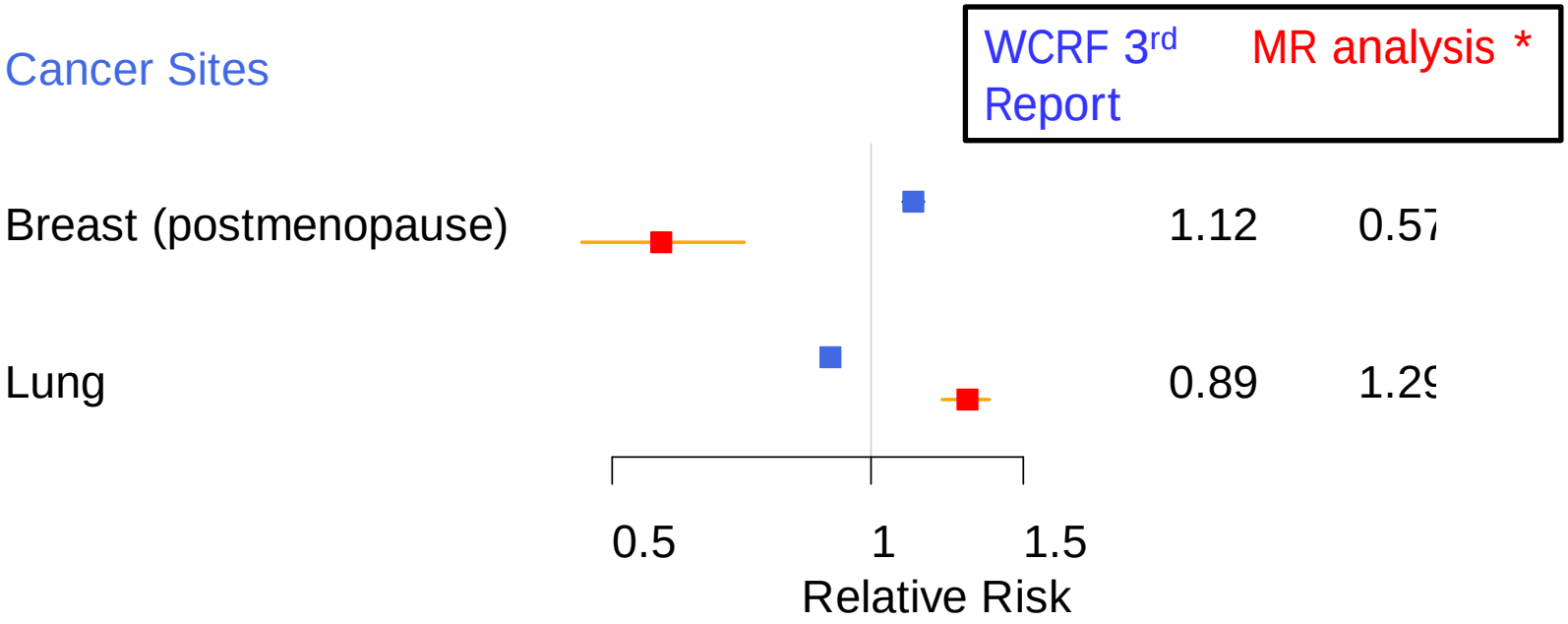


BMJ. 2018 May 16;

- Genetic analysis among over 400,000 individuals
- ‘Higher levels of obesity increase the risk of individuals taking up smoking, as well as smoking intensity’.

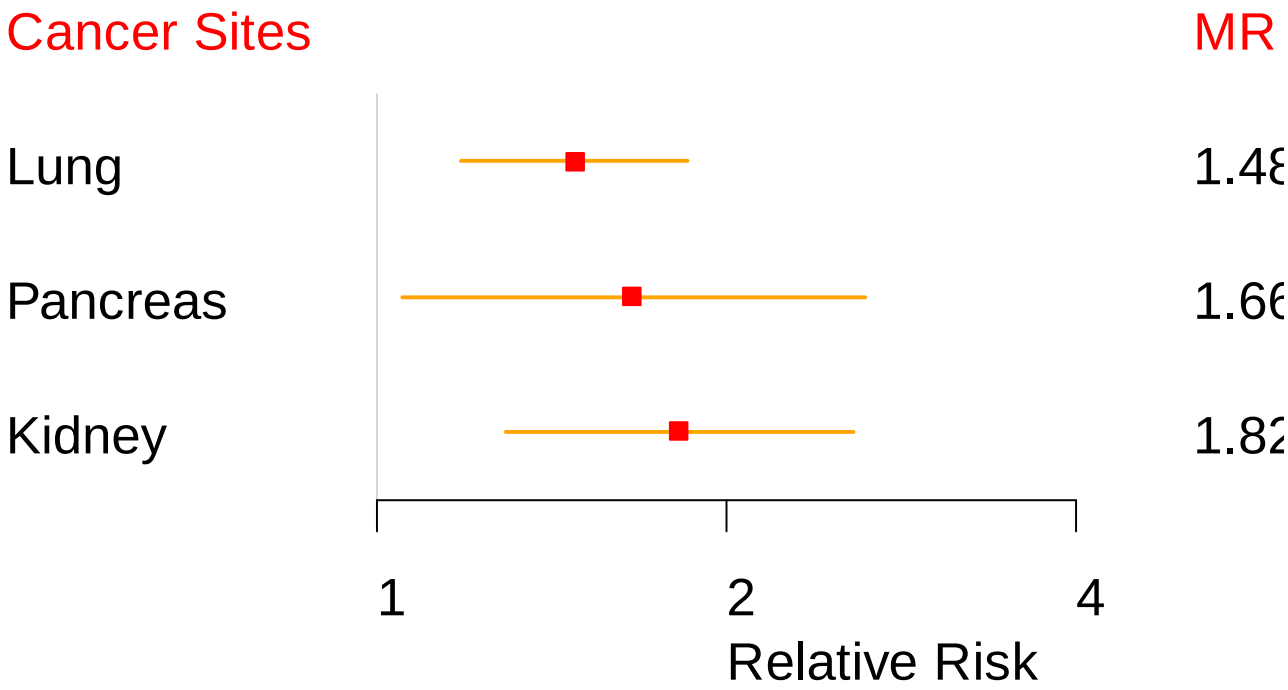
BMC. 2018 May 16;

Many potential uses of Mendelian randomization for cancer

- **Anthropometric - **BMI, etc
- **Behavior :** smoking, alcohol consumption, coffee consumption
- **Clinical conditions,** e.g. diabetes, insulin levels, lipids, hypertension, lung function etc
- **Circulating vitamins,** eg vitamin D, Vitamin B6, folate, B12…
- **Circulating metabolites and proteins,**
- **Drug targets….**eg PCSK9 inhibitors

- **Can look at the effect on disease outcome as well as onset**

Increased fasting insulin levels and cancer risk :
a Mendelian randomization analysis



Carreras-Torres et al. *PLoS One* 2017, Carreras-Torres et al. *JNCI* 2017, Johansson et al. submitted

Summary

- Genetics is playing an increasing and important contribution to our knowledge of the causes of cancer

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Summary

- Genetics is playing an increasing and important contribution to our knowledge of the causes of cancer
- This evidence is complimentary to other forms of evidence
- It has important potential to help fill in the missing 60%
- Lots more to come.....

Acknowledgements

International Agency for Research on Cancer (Lyon, France)

- Daniela Mariosa
- Robert Carreras-Torres
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CRUK “Reducing the burden of cancer” (PI: R Martin & C Relton)

Bridging the cancer genetics divide:

Considerations for low and middle income countries

Ophira Ginsburg MSc MD

High-Risk Cancer Genetics Program, Perlmutter Cancer Center

Section for Global Health, Department of Population Health

NYU Langone Health

World Cancer Congress
Kuala Lumpur, Malaysia
1—4 Oct 2018

Strengthen
Inspire
Deliver

uicc
global cancer control
WORLD CANCER CONGRESS

Track 2 - Advances in screening and early detection

Disclosure of interest: None declared

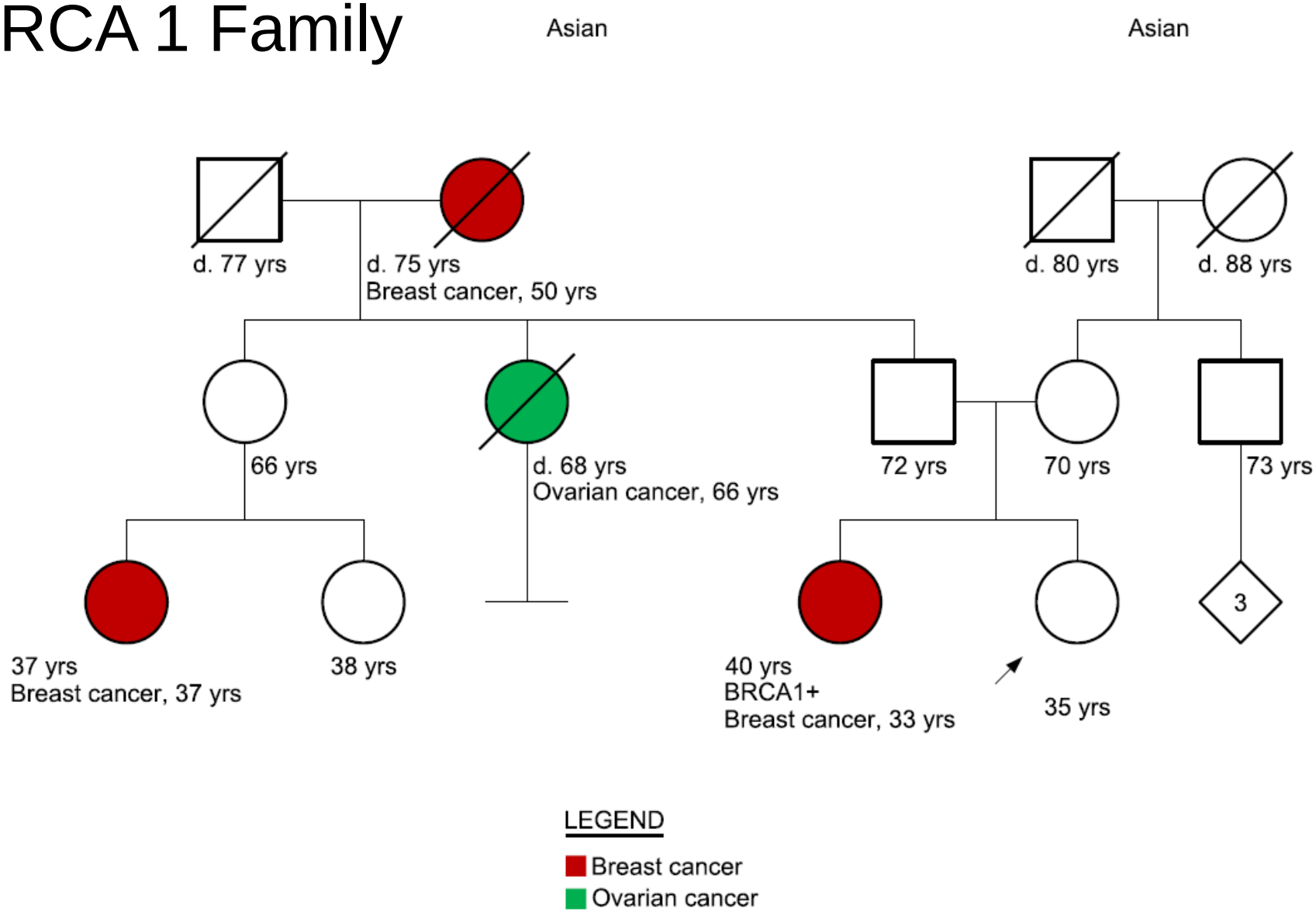
Objectives:

- To have a basic understanding of the common hereditary cancer syndromes, and to be aware of rapidly changing evidence-informed guidelines for testing and clinical management.

- To know the concepts of multigene panels, tumor/normal sequencing (NGS), and the expanding and critical role(s) of well-trained providers such as the cancer genetic counselor.

- To consider what core elements are needed to ensure that a cancer genetics service can provide high quality comprehensive patient care, that is “reasonable” for a given context and health system.

BRCA 1 Family



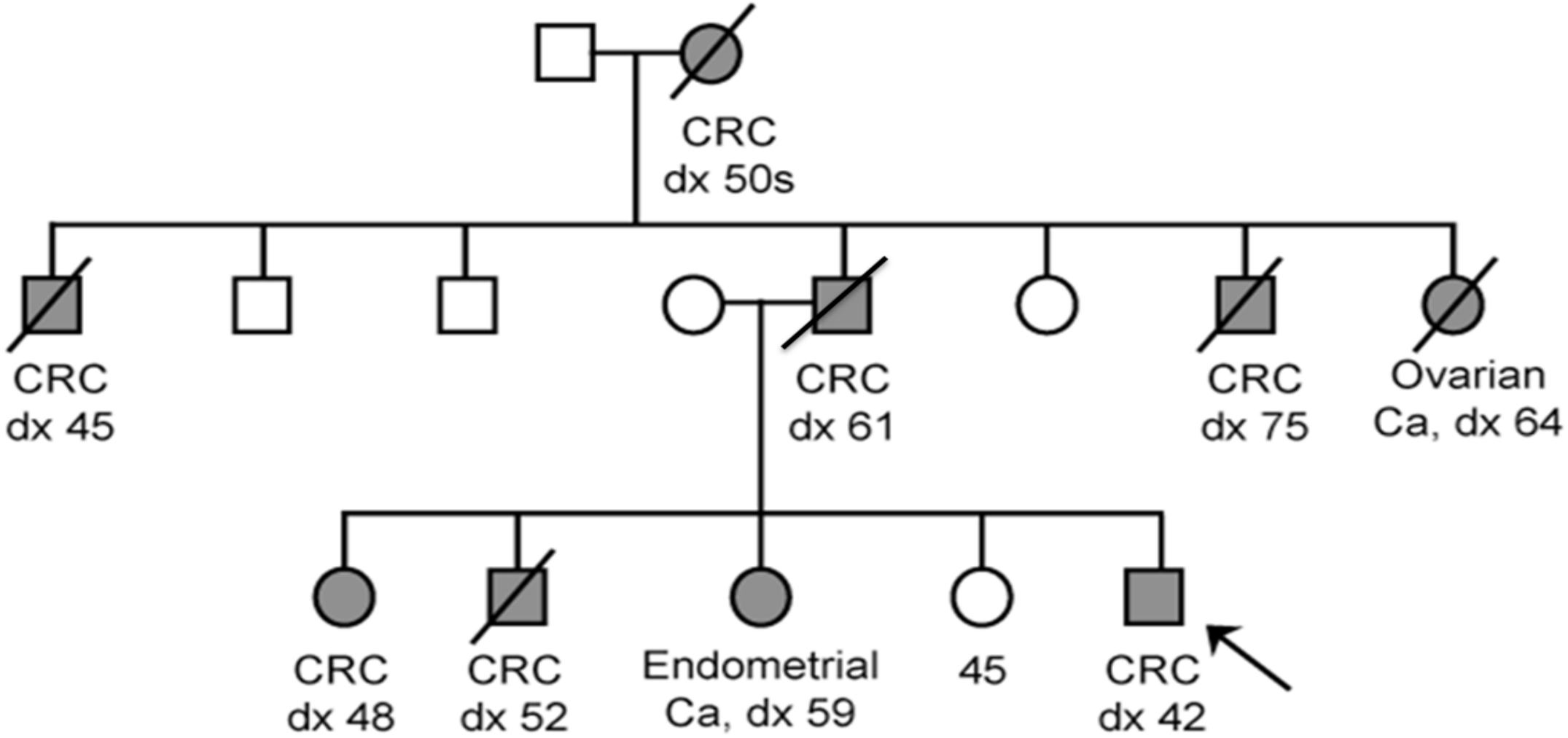
Frequency:

General population: 1/500-1/700

Ashkenazi Jewish: 1/40

Pedigree modified to protect confidentiality

Lynch Syndrome

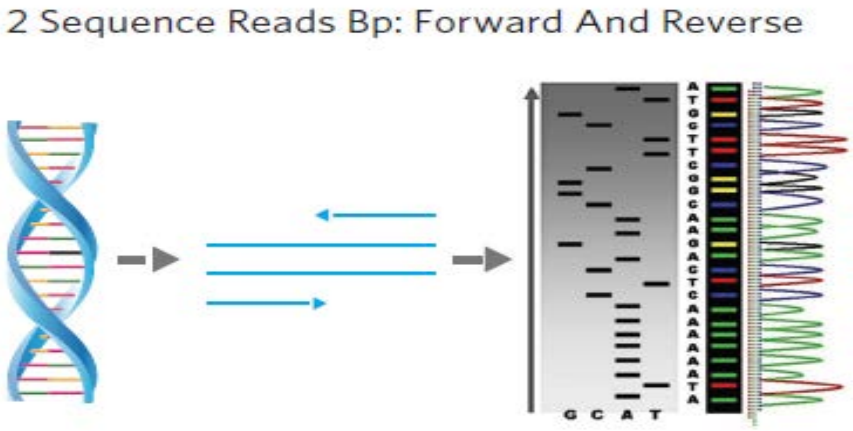


Sanger Sequencing

Gold standard since 1970s

Two reads per DNA position

Used for single gene testing and confirmatory testing



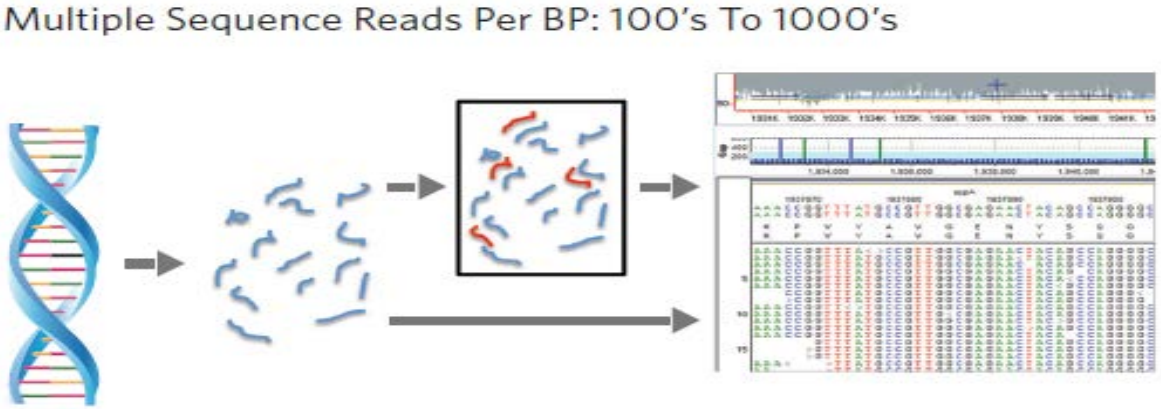
Next-Generation Sequencing

Clinically available in 2010

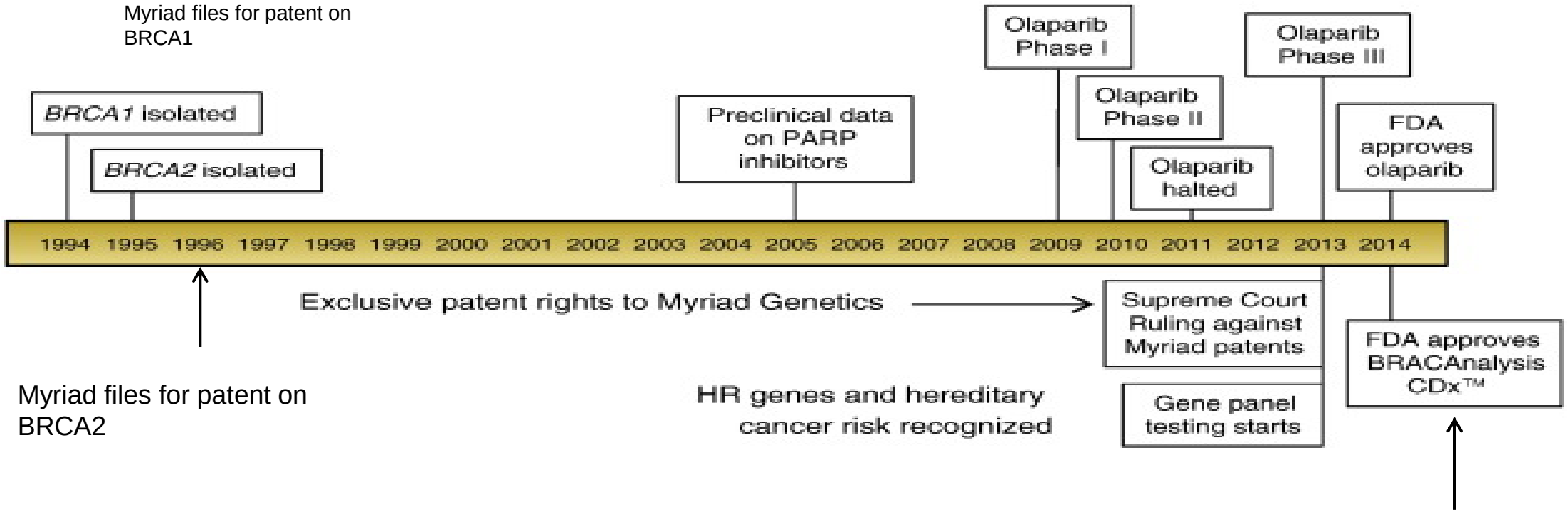
Simultaneous reading for each targeted position

Used for multi-gene testing and high throughput data

Cost effective for more than one gene analyzed



http://www.ambrygen.com/sites/default/files/Optimizing_Technology_White_Paper_10_13_14final.pdf



2015- patients tested before 8/2015 are eligible for update panel testing at Myriad

Modified from Walsh, 2015

“Multigene testing is ideally ordered in the context of professional genetic expertise for pre- and post-test counseling…. for risk prediction, risk reduction for patient & family members, tailored TREATMENT options”

NCCN 2018….

Hereditary Cancer Multigene Panels

BRCAplus 8 genes	BreastNext 17 genes	GYNplus 13 genes	OvaNext 25 genes	ColoNext 17 genes	ProstateNext 14 genes	PancNext 13 genes	CancerNext 34 genes	BrainTumorNext 27 genes	MelanomaNext 8 genes	RenalNext 19 genes	PGLNext 12 genes	CancerNext-Exp 67 genes	CustomNext-Cancer up to 81 genes
	BARD1		BARD1				BARD1					BARD1	BARD1
	BRIP1	BRIP1	BRIP1				BRIP1					BRIP1	BRIP1
	MRE11A		MRE11A				MRE11A					MRE11A	MRE11A
	NBN		NBN		NBN		NBN	NBN				NBN	NBN
	NF1		NF1				NF1	NF1			NF1	NF1	NF1
	RAD50		RAD50				RAD50					RAD50	RAD50
	RAD51C	RAD51C	RAD51C				RAD51C					RAD51C	RAD51C
	RAD51D	RAD51D	RAD51D		RAD51D		RAD51D					RAD51D	RAD51D
ATM	ATM		ATM		ATM	ATM	ATM					ATM	ATM
PALB2	PALB2	PALB2	PALB2		PALB2	PALB2	PALB2					PALB2	PALB2
	MUTYH		MUTYH	MUTYH			MUTYH					MUTYH	MUTYH
CHEK2	CHEK2		CHEK2	CHEK2	CHEK2		CHEK2					CHEK2	CHEK2
			STK11	STK11		STK11	STK11					STK11	STK11
CDH1	CDH1		CDH1	CDH1			CDH1					CDH1	CDH1
BRCA1	BRCA1	BRCA1	BRCA1		BRCA1	BRCA1	BRCA1					BRCA1	BRCA1
BRCA2	BRCA2	BRCA2	BRCA2		BRCA2	BRCA2	BRCA2		BRCA2			BRCA2	BRCA2
PTEN	PTEN	PTEN	PTEN	PTEN			PTEN	PTEN	PTEN	PTEN		PTEN	PTEN
TP53	TP53	TP53	TP53	TP53	TP53	TP53	TP53	TP53	TP53	TP53		TP53	TP53
		MLH1	MLH1	MLH1	MLH1	MLH1	MLH1	MLH1		MLH1		MLH1	MLH1
		MSH2	MSH2	MSH2	MSH2	MSH2	MSH2	MSH2		MSH2		MSH2	MSH2
		MSH6	MSH6	MSH6	MSH6	MSH6	MSH6	MSH6		MSH6		MSH6	MSH6
		PMS2	PMS2	PMS2	PMS2	PMS2	PMS2	PMS2		PMS2		PMS2	PMS2
		EPCAM	EPCAM	EPCAM	EPCAM	EPCAM	EPCAM			EPCAM		EPCAM	EPCAM
			SMARCA4				SMARCA4	SMARCA4				SMARCA4	SMARCA4
				APC		APC	APC	APC				APC	APC
				BMPR1A			BMPR1A					BMPR1A	BMPR1A
				SMAD4			SMAD4					SMAD4	SMAD4
						CDKN2A	CDKN2A	CDKN2A	CDKN2A			CDKN2A	CDKN2A
							CDK4		CDK4			CDK4	CDK4
				GREM1			GREM1					GREM1	GREM1
				POLD1			POLD1					POLD1	POLD1
				POLE			POLE					POLE	POLE
					HOXB13		HOXB13					HOXB13	HOXB13
			DICER1				DICER1	DICER1				DICER1	DICER1

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 2.2019 — July 30, 2018

NCCN.org

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Breast and/or Ovarian Cancer Genetic Assessment

NCCN Guidelines Index
Table of Contents
Discussion

CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene within the family, including such variants found on research testing[b]
- An individual at any age with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene found on tumor testing (See BR/OV-A 3 of 3)
- An individual diagnosed at any age with any of the following:
  - Ovarian cancer[c]
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - Breast cancer or high-grade (Gleason score ≥7) prostate cancer and of Ashkenazi Jewish ancestry
- An individual with a breast cancer diagnosis meeting any of the following:
  - Breast cancer diagnosed age ≤50 y
  - Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age ≤60 y
  - Two breast cancer primaries[e]
  - Breast cancer at any age, and
    - ≥1 close blood relative[f] with:
      - breast cancer age ≤50 y; or
      - invasive ovarian cancer[c]; or
      - male breast cancer; or
      - pancreatic cancer; or
      - high-grade (Gleason score ≥7) or metastatic prostate cancer[d]
    - ≥2 close blood relatives[f] with breast cancer at any age
- An individual who does not meet the above criteria but has a first- or second-degree relative with any of the following:[g]
  - Breast cancer ≤45 y
  - Ovarian[b] cancer
  - Male breast cancer
  - Pancreatic cancer
  - Metastatic prostate cancer[d]
  - ≥2 breast cancer primaries in a single individual
  - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
- An individual with a personal and/or family history on the same side of the family of three or more of the following (especially if diagnosed age ≤50 y; can include multiple primary cancers in same individual):[g]
  - breast cancer, sarcoma, adrenocortical carcinoma, brain tumor, leukemia (see LIFR-1),
  - colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations,[h] macrocephaly, or hamartomatous polyps of gastrointestinal (GI) tract (see COWD-1),
  - lobular breast cancer, diffuse gastric cancer (see CDH1 guidelines, GENE-2),
  - breast cancer, gastrointestinal cancer or hamartomatous polyps, ovarian sex chord tumors, pancreatic cancer, testicular sertoli cell tumors, or childhood skin pigmentation (see STK11 guidelines, GENE-4)

→ Consider referral to cancer genetics professional[i] → See Assessment (BR/OV-2)

[a] The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

[b] Irrespective of degree of relatedness.

[c] Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

[d] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence.

[e] Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors diagnosed either synchronously or asynchronously.

[f] Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-B).

[g] When possible, genetic testing should be performed first on an affected family member.

[h] For dermatologic manifestations, see COWD-1.

[i] For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

Note: 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.

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling).[1-5] A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in the counseling of patients.

• Pre-test counseling includes: ‣ Collection of a comprehensive family history ◊ Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family (See BR/OV-B) ‣ Evaluation of a patient's cancer risk ‣ Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity ‣ Preparing the patient for possible outcomes of testing including positive (pathogenic, likely pathogenic), negative, and uncertain findings and obtaining informed consent	• Post-test counseling includes discussions of: ‣ Results along with their significance and impact and recommended medical management options ‣ Interpretation of results in context of personal and family history of cancer ‣ Informing and testing at-risk family members ‣ Available resources such as disease-specific support groups and research studies

Genetic Testing Considerations

- Testing should be considered in appropriate high-risk individuals where it will impact the medical management of the tested individuals and/or their at-risk family members. It should be performed in a setting in which it can be adequately interpreted.[1]
- The probability of pathogenic/likely pathogenic variant detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial pathogenic/likely pathogenic variant detection. The estimated likelihood of pathogenic/likely pathogenic variant detection may be very low in families with a large number of unaffected female relatives.
- Patients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA until other technologies are available. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.
- Comprehensive genetic testing includes full sequencing and testing for large genomic rearrangements. It is encouraged that testing be done in commercial or academic labs that are clinically approved and validated. See BR/OV-A 3 of 3.
- In children <18 y, genetic testing is generally not recommended when results would not impact medical management.[6]
- Likely pathogenic variants are often treated similarly to pathogenic variants.

Continued

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility

Mark E. Robson, Angela R. Bradbury, Banu Arun, Susan M. Domchek, James M. Ford, Heather L. Hampel, Stephen M. Lipkin, Sapna Syngal, Dana S. Wollins, and Noralane M. Lindor

3 technical considerations for policymakers:

✓Analytical validity (NB/ high rates of discordance btw commercial labs)

✓Clinical validity (reliable evidence of strength of association)

✓Clinical utility (proven /evidence for the information leading to prevention/screening or Rx that impacts health – not always clear)

accompanying editorial:

“New technology is introducing great complexity”

#understatementoftheyear

JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Genetic Testing for Breast Cancer in the Era of Multigene Panels: Can We Make an Impact on Population Health?

Ophira Ginsburg, *Perlmutter Cancer Center NYU Langone Health, New York, NY*
Paul Brennan, *International Agency for Research on Cancer, Lyon, France*

See accompanying article doi:https://doi.org/10.1200/JCO.2018.78.3977

Technical, regulatory, and health systems considerations

1. What is understood about the acceptability of genetic testing for hereditary cancer in a community? (stigma about cancer, about hereditary disease)

2. Does ”testing” include comprehensive education and pos-test counseling by trained providers? (many ordering providers in U.S. get this wrong!)

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Technical, regulatory, and health systems considerations

3. Who will interpret variants of uncertain significance? (can be v complicated)

4. Work force and technical capacities for risk-reduction interventions? (if access to timely, affordable, good quality diagnostic imaging, pathology, screening, and surgery is limited, why offer testing?)

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Technical, regulatory, and health systems considerations

5. Have ethical, legal, and regulatory frameworks to protect personal and to protect individuals from genetic discrimination? (”GINA” like legislation?)

6. Is the health system funded well enough to support cancer genetics services? (what % GDP is spent on health? Public/private?)

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Questions?
Thank you!

Are we ready for population-wide germline genetic testing? An example from Brazil

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Universidade Federal do Rio Grande do Sul, Brazil
Rede Brasileira de Câncer Hereditário

World Cancer Congress
Kuala Lumpur, Malaysia
1—4 Oct 2018

Strengthen
Inspire
Deliver

uicc
global cancer control
WORLD CANCER CONGRESS

•Track 2: Advances in screening and early detection

Disclosure of interest: None declared

Objectives

- To review the basic epidemiology of breast cancer in Brazil and fundamentals of hereditary breast cancer;
- To review statistics of a founder *TP53* germline mutation, R337H, in Southern Brazil and its role in breast cancer predisposition;
- To consider pros and cons of population testing for R337H and what questions must be answered in order to enable adequate testing and management of mutation carriers in the long term.

Estimated age-standardized incidence rates (World) in 2018, breast, all ages

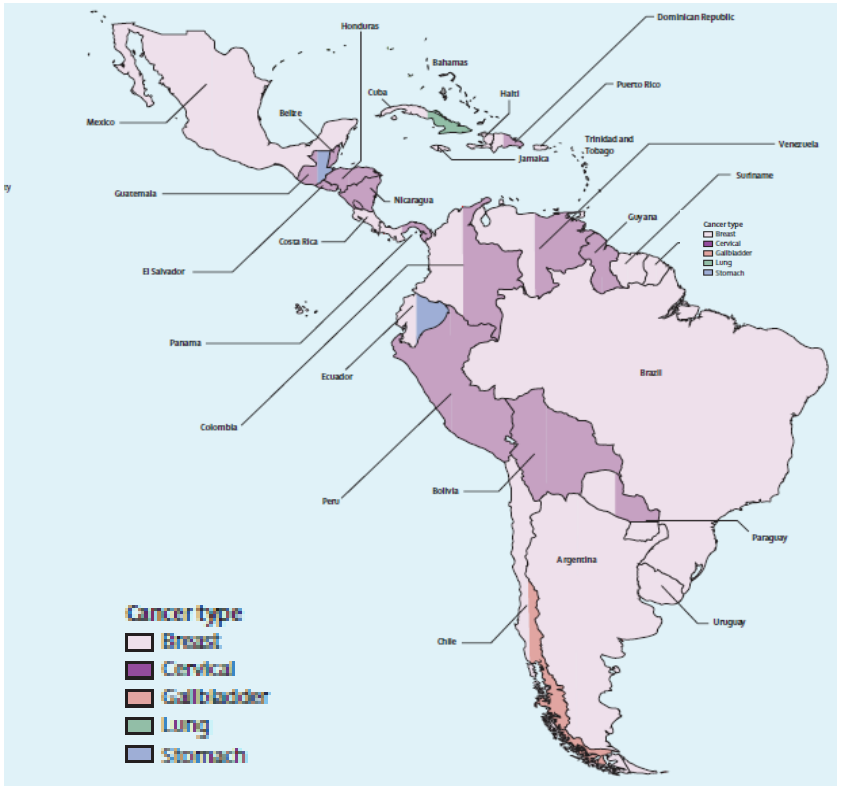
ASR (World) per 100 000

- ≥ 69.0
- 51.4–69.0
- 39.4–51.4
- 26.3–39.4
- < 26.3
- Not applicabl
- No data

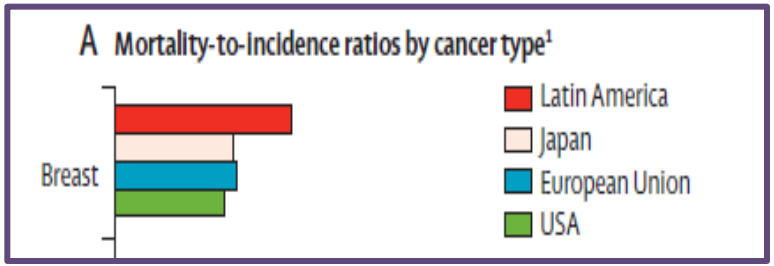
https://gco.iarc.fr

Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

Breast Cancer
in Latin America and Brazil



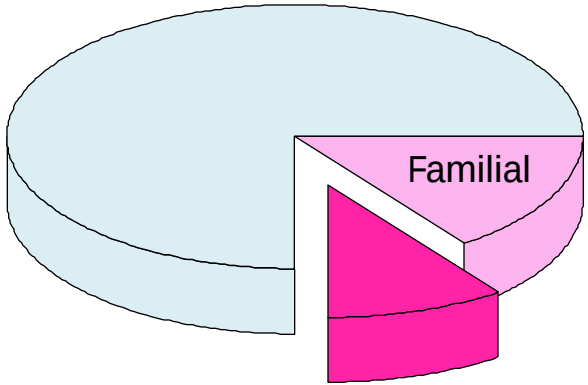
Lancet Oncol 2013; 14: 391–436



- ✓ Most common cancer in women;
- ✓ 59.700 new breast cancer cases are estimated in 2018;

- ✓ Adjusted incidence rates
  - Entire country: 51,33/100.000
  - South region: 73,07/100.000

At least 10% of all Breast Cancers are Hereditary



10% of breast cancers are hereditary

Penetrance: moderate - high; germline mutations cause a well known cancer syndrome.

Allele frequency: very low - low.

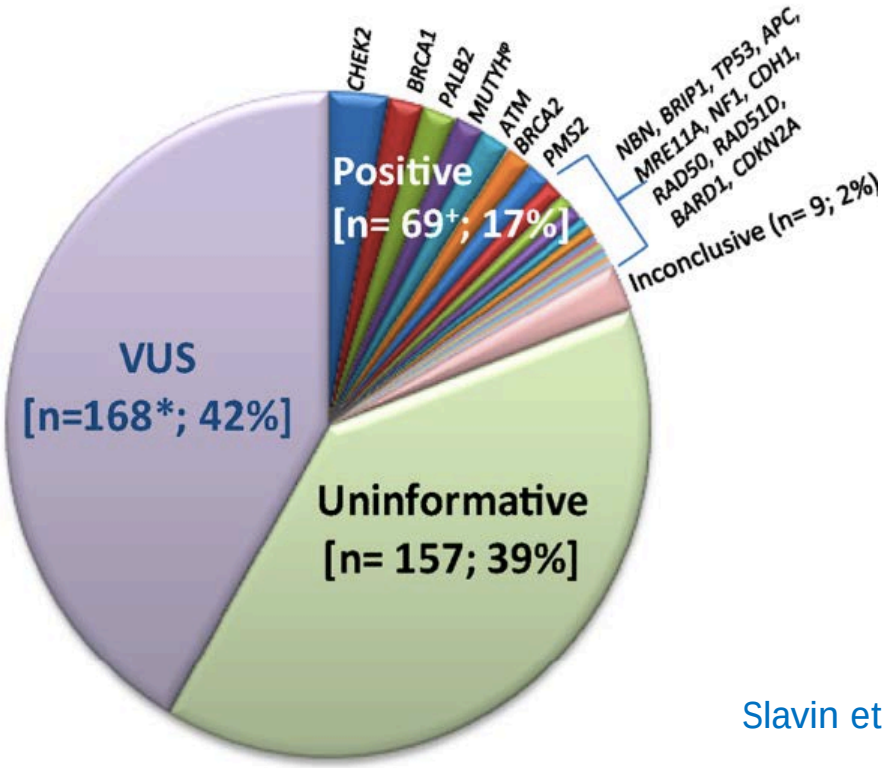
OR for breast cancer: > 5.0.

Actionability: high; evidence based risk reducing guidelines exist.

Implications for other family members: well defined.

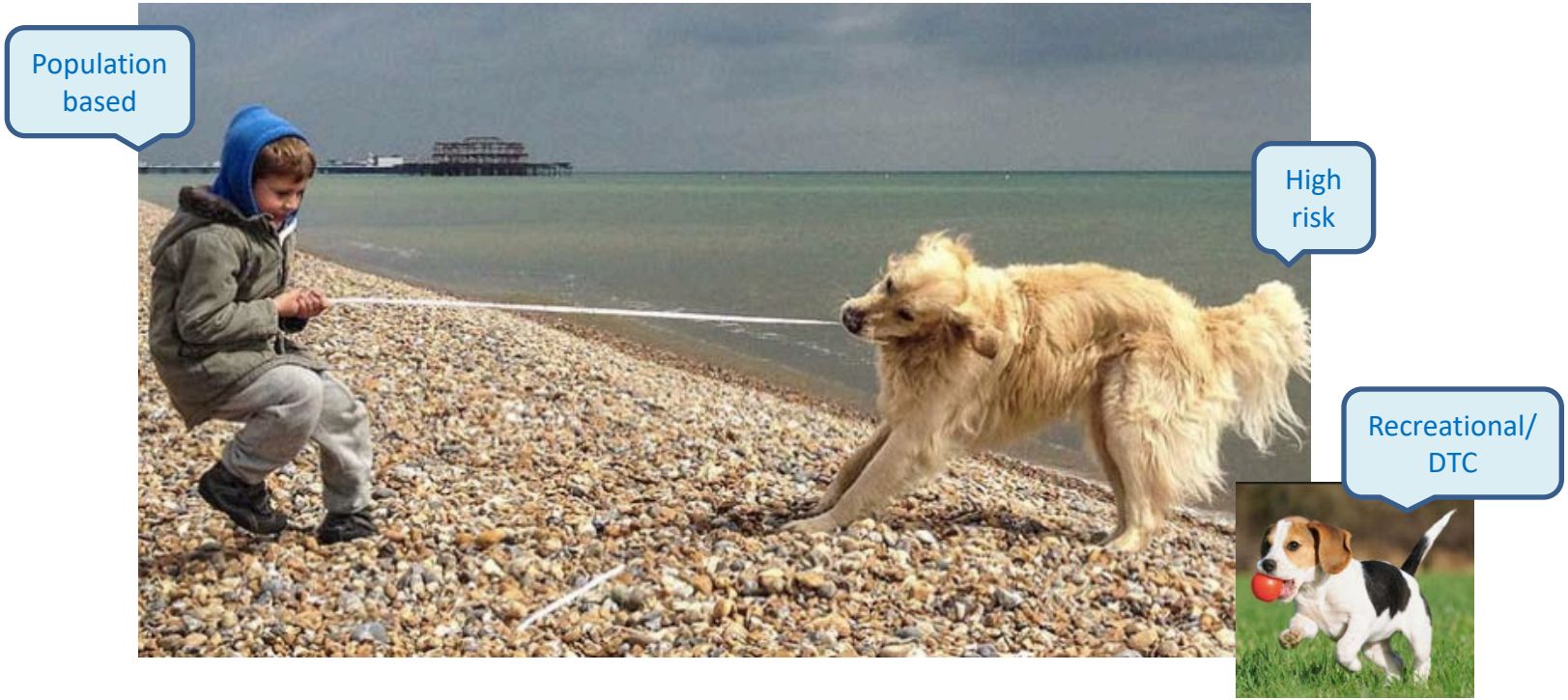
Genetic Heterogeneity of Hereditary Breast Cancer: Multigene Panel Testing

GENE	N	% of all Positives
CHEK2	12	17.4
BRCA1	7	10.1
PALB2	7	10.1
MUTYH$^{\varphi}$	6	8.7
ATM	6	8.7
BRCA2	5	7.2
PMS2	5	7.2
NBN	4	5.8
BRIP1	3	4.3
p53	3	4.3
APC	2	2.9
MSH6	2	2.9
MRE11A	1	1.4
NF1	1	1.4
CDH1	1	1.4
RAD50	1	1.4
RAD51D	1	1.4
BARD1	1	1.4
CDKN2A	1	1.4



Slavin et al. 2015

Best genetic testing approach: high risk testing vs. population testing ?



Southern Brazilian Founder Mutation
TP53 c. 1010G>A (p.Arg337His)

Health-care Development

2009

Highly prevalent *TP53* mutation predisposing to many cancers in the Brazilian population: a case for newborn screening?

Maria Isabel Waddington Achatz, Pierre Hainaut, Patricia Ashton-Prolla

About **1:300** newborns in Southern Brazil carry *TP53* R337H

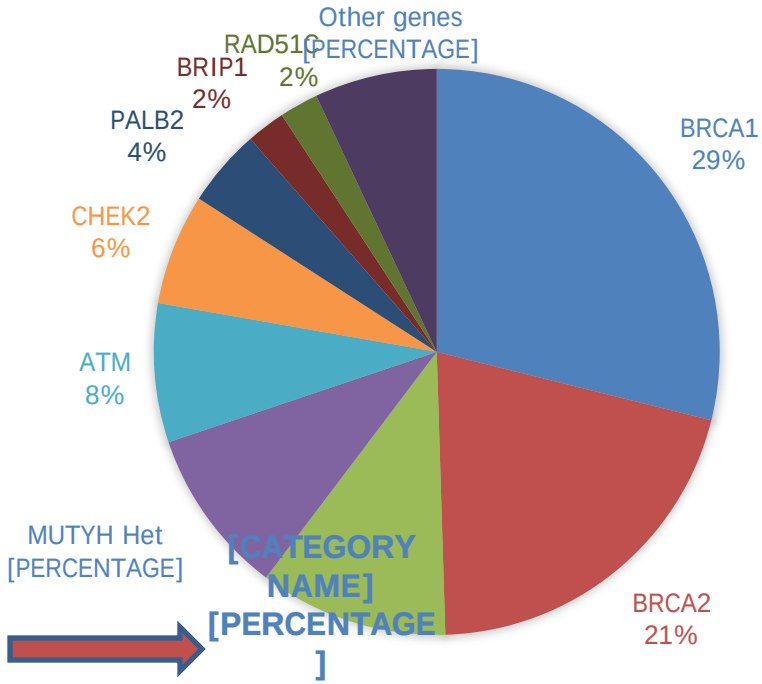
Adrenocortical carcinoma screening offered until age 15 ys

Wilson & Jungner Criteria for Newborn Screening (1968): applied to *TP53* R337H

	Criteria met?
Condition to be screened should be a significant health problem	Yes
The natural history of the condition should be well known	No
Condition should have a detectable preclinical phase	Yes
Early detection should be beneficial compared with late detection	Yes
An appropriate test should be available for application during the early phase	Yes
Test must follow an accepted procedure	Yes
Benefits must outweigh physical and psychological risks	Not assessed
Costs must be modest compared with benefits	Not assessed

TP53 mutations and breast cancer in Brazil

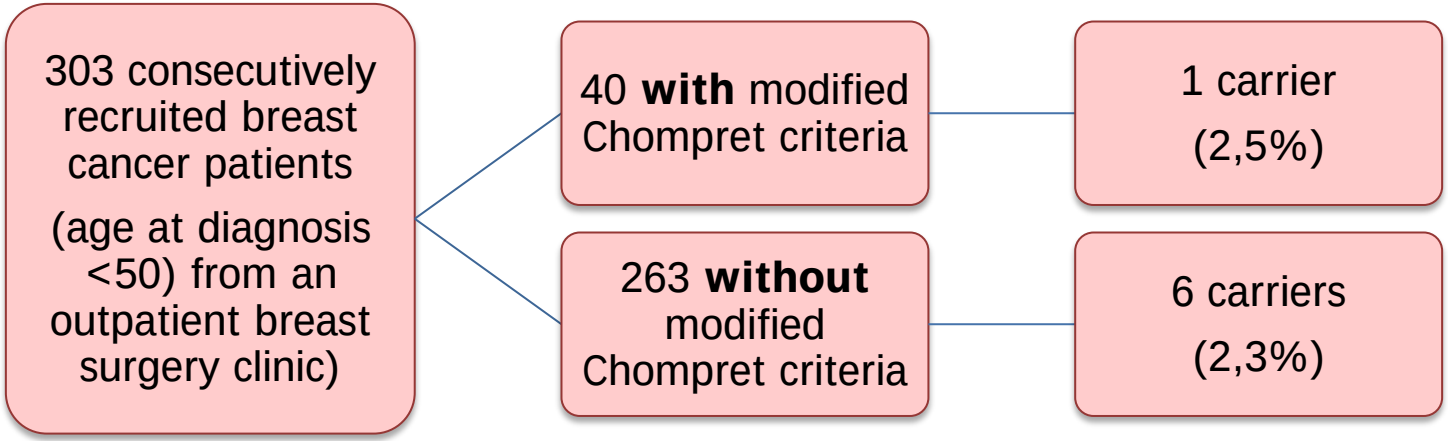
Pathogenic/Likely Pathogenic variants in 1554 hereditary breast cancer patients in Brazil (Multigene panel testing)



Most (70%) are R337H

Guindalini RS *et al*, unpublished

TP53 c. 1010G>A (p.Arg337His) and Breast Cancer in Southern Brazil



1/43 early onset BC patients in this series is an R337H carrier;
Chompret criteria for *TP53* testing are insufficient to detect most carriers.

Camila Bittar, preliminary results, unpublished

Should all women with early onset breast cancer in Southern Brazil be tested for R337H ?

Why not ?
Mutation frequency is high and criteria-based testing will likely miss most carriers.

And what about population screening in asymptomatic individuals ?

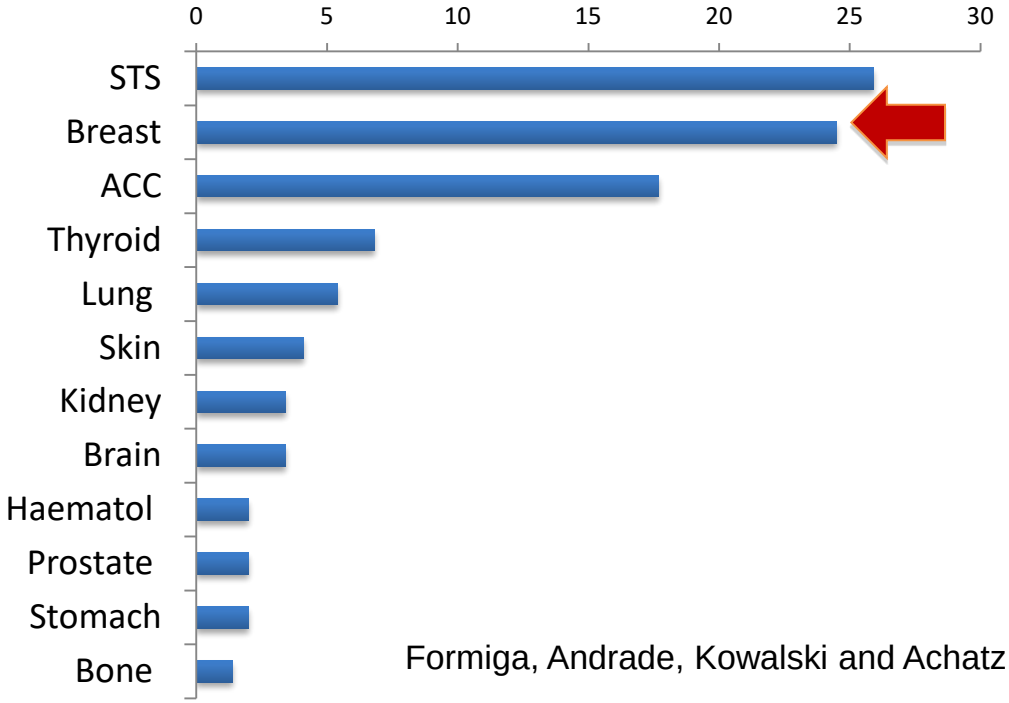
JAMA Oncology

Research

Frequency of Thyroid Carcinoma in Brazilian *TP53* p.R337H Carriers With Li Fraumeni Syndrome

Maria Nirvana da Cruz Formiga, MD; Kelvin César de Andrade, MSc;
Luiz Paulo Kowalski. MD. PhD: Maria Isabel Achatz. MD. PhD

JAMA Oncol. 2017;3(10):1400-1402. doi:10.1001/jamaoncol.2016.6389



NIH NATIONAL CANCER INSTITUTE
Division of Cancer Epidemiology & Genetics

Formiga, Andrade, Kowalski and Achatz. JAMA Oncology, 2017.

In conclusion

- ✓ Approach for *TP53* R337H mutation testing in Brazil must be urgently reviewed.
- ✓ Best setting ? pre-menopausal breast cancer patients (”diagnostic”)
  NB screening; asymptomatic young adults (”predictive”)
- ✓ Unanswered questions that must be addressed for successful long-term outcomes:

  - Prevalence of the mutation in the population (all 5 regions) ?
  - Penetrance (Breast cancer; who will get pediatric/adult onset cancers) ?
  - Feasibility of population-wide testing, counseling and screening of carriers, including acceptance within the population.

BREAST CANCER AWARENESS MONTH

Thank you !