Curso

Medicina Personalizada de Precisión

De la teoría
a la práctica

Fundación InstitutoRoche

De la Biología Molecular a la Medicina: Fundamentos de la Medicina Personalizada de Precisión

Miguel Urioste
Unidad Clínica de Cáncer Familiar
CNIO

Cathy, a 40-year-old mother of three, arrives in your office for her annual physical.

She has purchased a commercial genomewide scan (see the Glossary), which she believes measures the clinically meaningful risk that common diseases will develop, and has completed her family history online using My Family Health Portrait (www.familyhistory.hhs.gov), a tool developed for this purpose by the U.S. Surgeon General.

Her genomewide scan suggests a slightly elevated risk of breast cancer, but you correctly recognize that this information is of unproven value in routine clinical care. On importing Cathy's family-history file, your office's electronic health record system alerts you to the fact that Cathy is of Ashkenazi Jewish heritage and has several relatives with breast cancer, putting her at heightened risk for the hereditary breast and ovarian cancer syndrome. The system prompts you to discuss Cathy's risk of breast and ovarian cancer during the visit. Considering both her family history and ancestry, you refer Cathy to a health care professional with advanced genetics training for consultation.

In the coming months Cathy elects to have her DNA tested for mutations in *BRCA1* and *BRCA2*, the genes associated with hereditary breast and ovarian cancer syndrome, and to undergo a mammographic examination. Although the results of her genetic tests are negative, her mammogram reveals a suspicious abnormality. A biopsy is performed, and breast cancer is detected. Surgery is successful. Pathological examination of tissue from the excised tumor reveals that it is positive for estrogen-receptor protein and negative for human epidermal growth factor receptor type 2 (HER2); the lymph glands are free of cancer cells. Genetic-expression profiling of the tumor indicates a relatively high risk of recurrent cancer, and Cathy elects to receive adjuvant chemotherapy followed by treatment with tamoxifen. Five years later, the cancer has not recurred.

Feero WG & Guttmacher AE. N Engl J Med, 2011

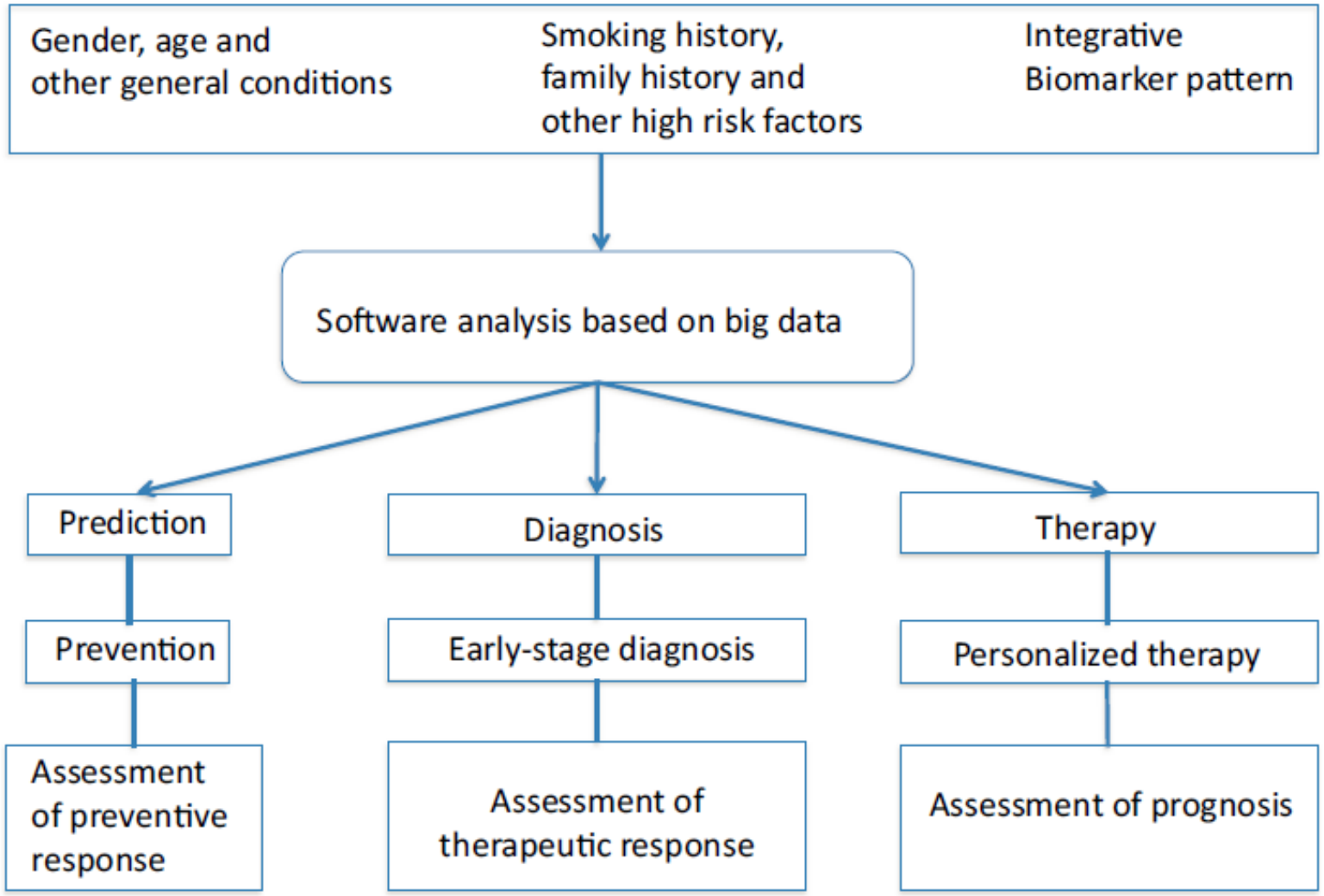
Precision Medicine Definition

Precision Medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

(The National Institutes of Health, USA)

Feero WG. JAMA, May 2017

Only focus on one aspect is not enough



Cheng T & Zhan X. EPMA Journal, 2017

Precision Medicine, no overall consensus

Table 3 Interview respondents' views on motivation for patient segmentation

Benefits	Experts
Avoiding side effects/optimize side effect profile	Academics (3), clinical experts (2), economic experts (3), EFPIA representative (1), patient representatives (2)
Avoiding waste of resources/over-treating/selecting only patients who need it	Academic (1), clinical experts (2), economic experts (3), EFPIA representative (1), patient representatives (2), payer (1)
Improved outcomes in terms of effectiveness/efficacy	Academic (1), clinical expert (1), economic experts (3), patient representative (1), payer (1)
Better outcome/benefit/response rate (not specified)	Academic (1), clinical experts (2), economic experts (2), provider (1)
Improved cost-effectiveness/value for money	Clinical expert (1), economic experts (3), payer (1)
Reduce costs	Economic experts (3), payer (1)
Improved length of life	Academic (1), clinical expert (1), economic expert (1)
Improved quality of life	Academic (1), economic expert (1)
Free-up time from clinicians	Patient representative (1), payer (1)

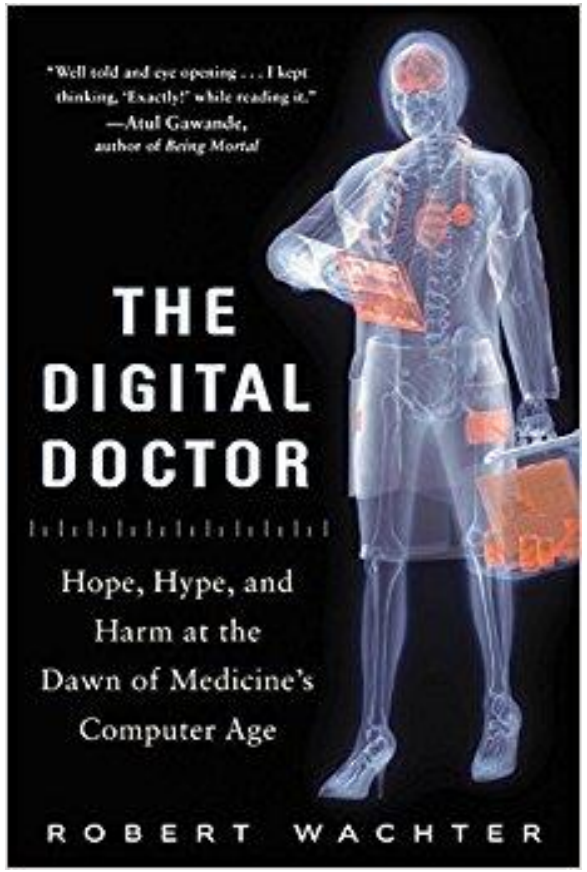
EFPIA, the European Federation of Pharmaceutical Industries and Associations

Di Paolo A et al. BMC Health Services Research, 2017

Precision Medicine is not a new concept

Hippocrates´ aphorism:

"It is more important to know the patient who has a disease, than the disease the patient has"



Sharrer GT. Methods Mol Biol, 2017

Precision Medicine is not a consensus strategy

VIEWPOINT

Seven Questions for Personalized Medicine

Michael J. Joyner, MD Nigel Paneth, MD, JAMA September 8, 2015

The precision-oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

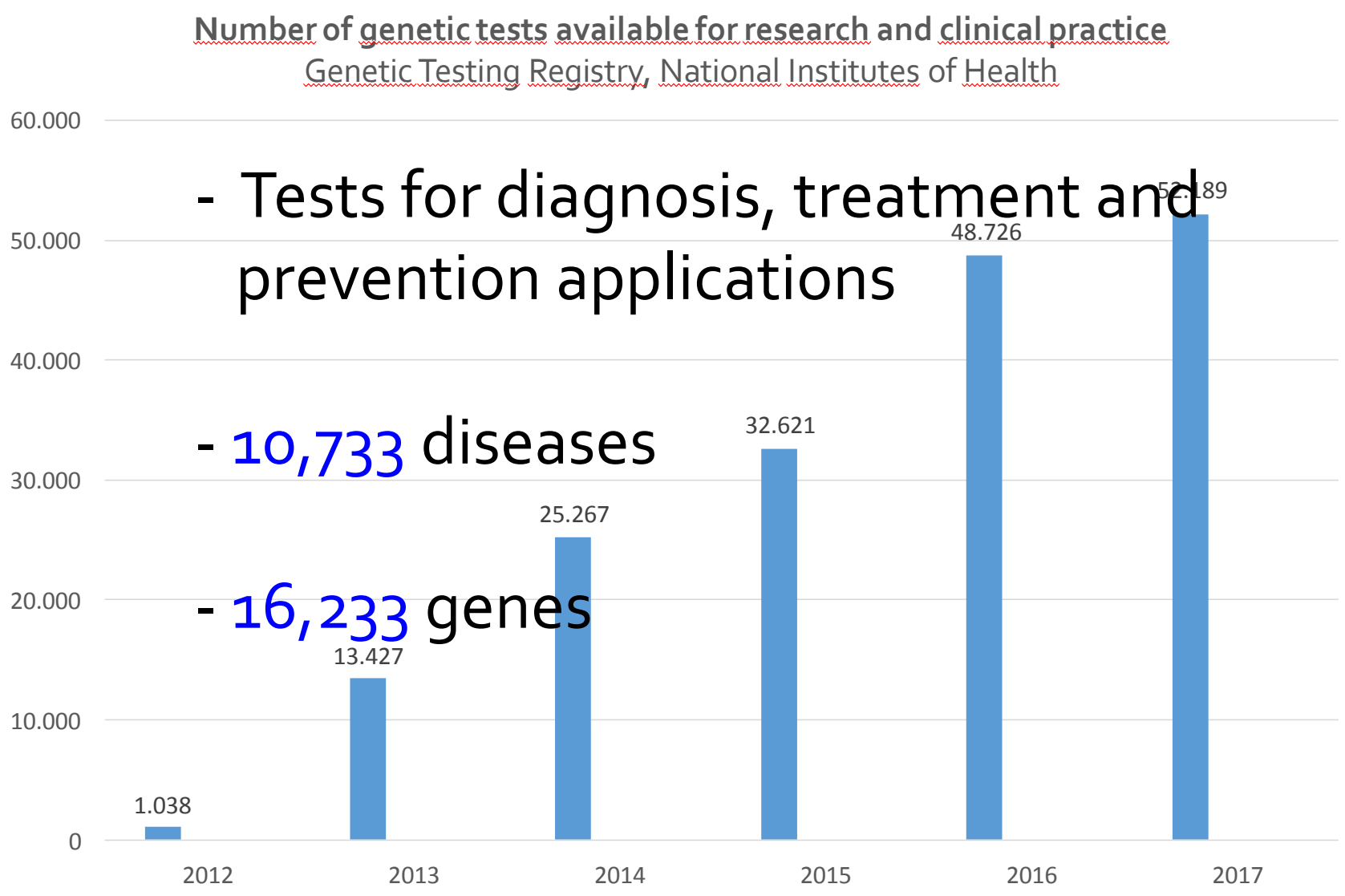
8 SEPTEMBER 2016 | VOL 537 | NATURE |

VIEWPOINT

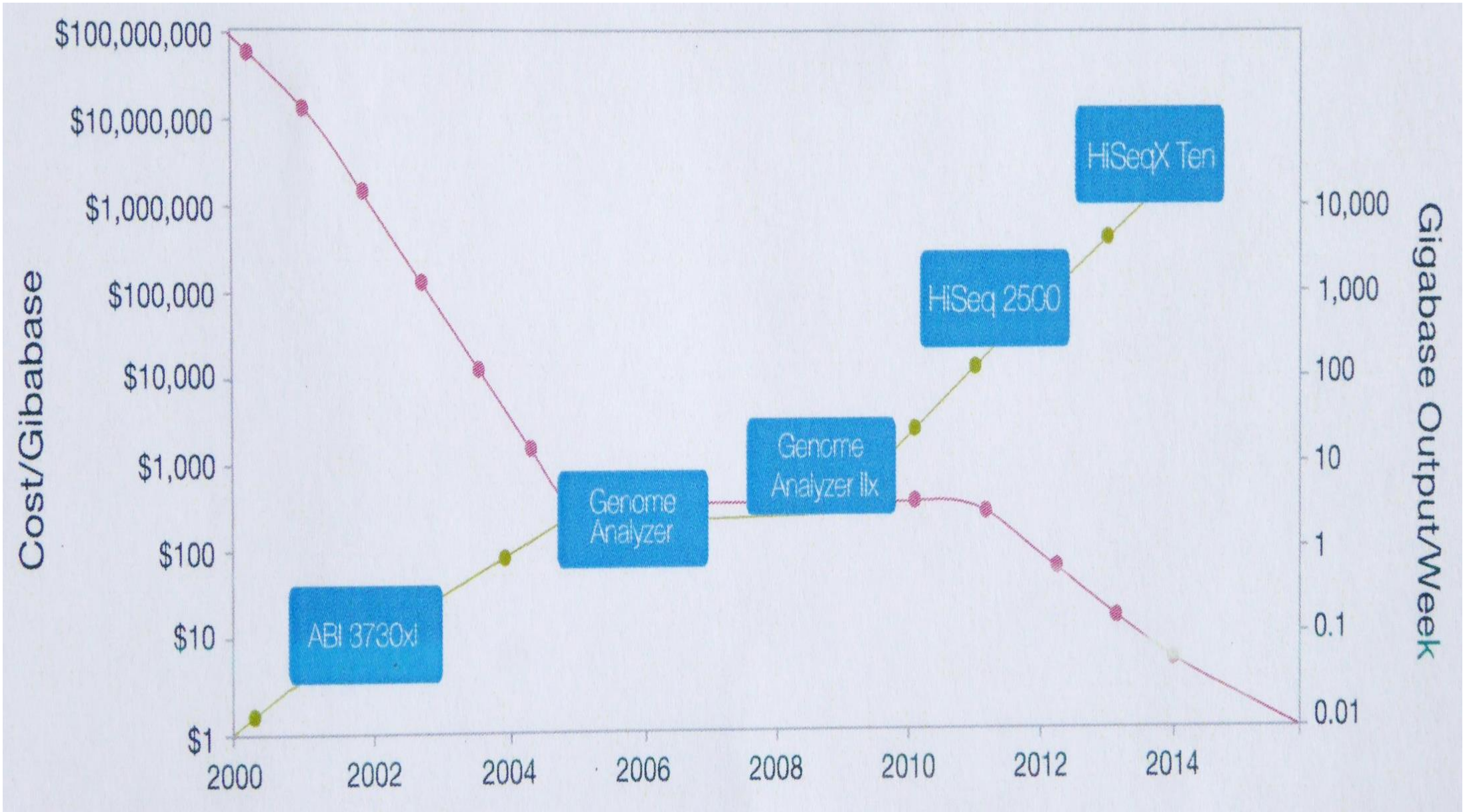
Will Precision Medicine Improve Population Health?

Muin J. Khoury, MD, Sandro Galea, MD, JAMA October 4, 2016


Science
THE HUMAN GENOME
nature
the human genome



"An Evidence Framework for Genetic Testing", The National Academies of Sciences, Engineering, and Medicine, Mar 2017



https://www.illumina.com/science/technology/next-generation-sequencing.html

This is historical material "frozen in time". The website is no longer updated and links to external websites and some internal pages may not work.

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THE PRECISION MEDICINE INITIATIVE

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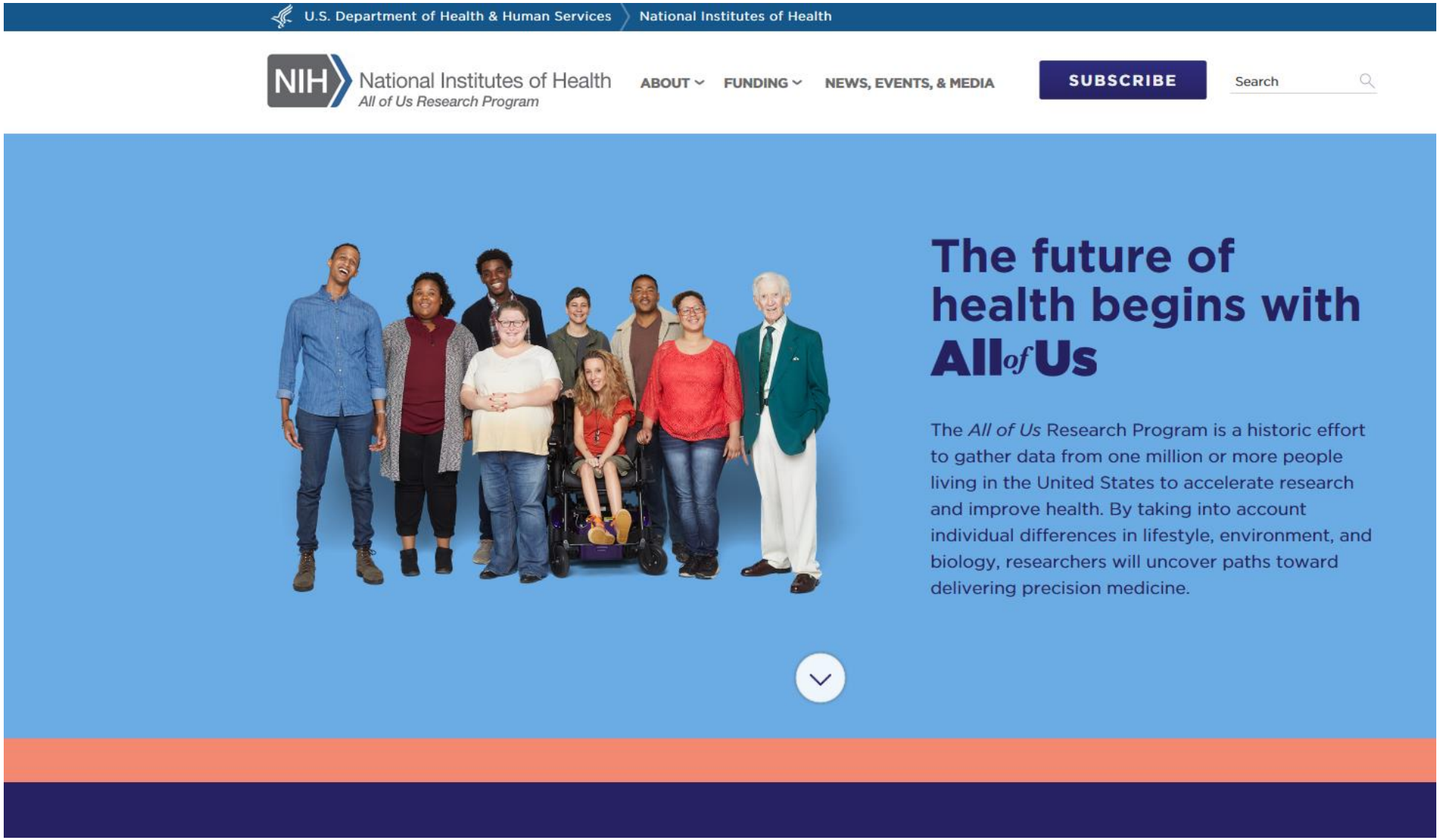

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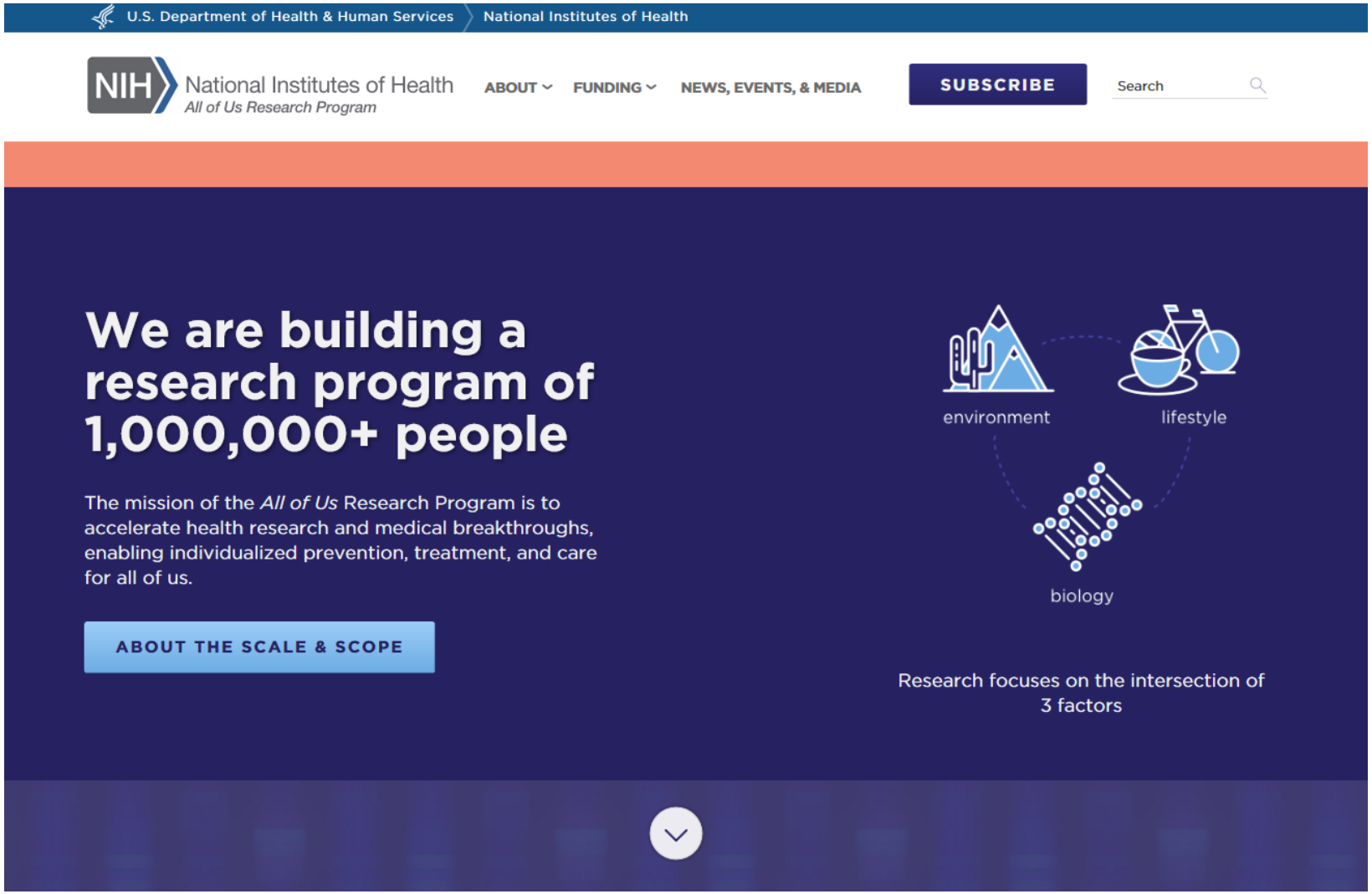

https://allofus.nih.gov/

NIH NATIONAL CANCER INSTITUTE

Español

1-800-4-CANCER Live Chat Publications Dictionary

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Home > Research > Key Initiatives

CANCER MOONSHOT℠

- Blue Ribbon Panel +
- Implementation
- Funding Opportunities +

Cancer Moonshot℠

The Cancer Moonshot to accelerate cancer research aims to make more therapies available to more patients, while also improving our ability to prevent cancer and detect it at an early stage.

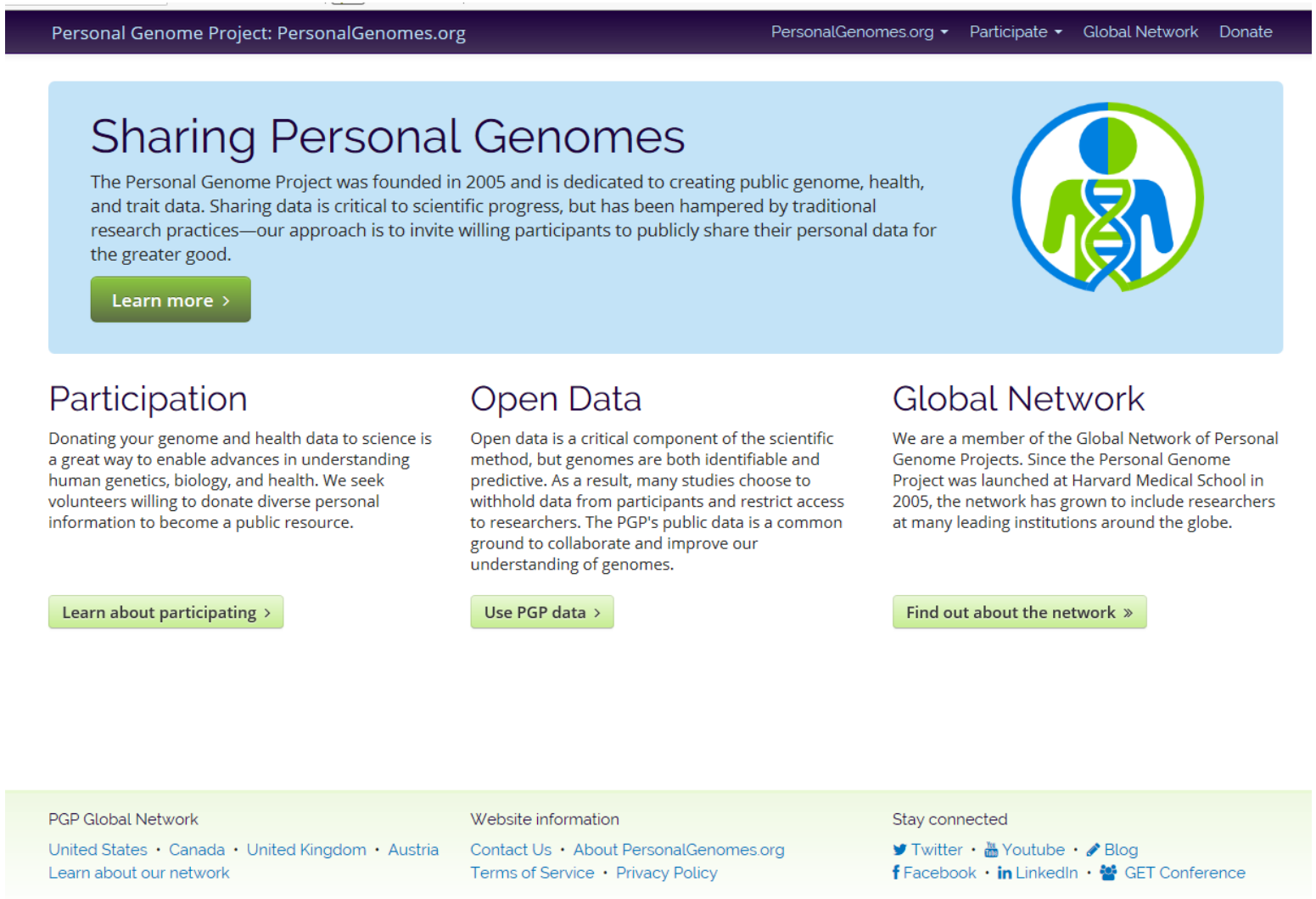
To ensure that the Cancer Moonshot's goals and approaches are grounded in the best science, a Cancer Moonshot Task Force consulted with external experts, including the presidentially appointed National Cancer Advisory Board (NCAB).

A Blue Ribbon Panel of experts was established as a working group of the NCAB to assist the board in providing this advice. The panel's charge was to provide expert advice on the vision, proposed scientific goals, and implementation of the Cancer Moonshot.

Congress passed the 21st Century Cures Act in December 2016 authorizing $1.8 billion in funding for the Cancer Moonshot over 7 years. An initial $300 million has been appropriated in fiscal year (FY) 2017 to fund Moonshot initiatives.

Get email updates from NCI on the Cancer Moonshot

https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative



http://www.personalgenomes.org/

ICPerMed
INTERNATIONAL CONSORTIUM

ICPerMed Action Plan

The ICPerMed Action Plan sets out a discrete set of research and research-supporting activities that will feed into national and European strategic discussion of research funding. **>> read more**

ICPerMed Workshop 2017

The first ICPerMed workshop took place on 26-27 June 2017 in Milan, Italy. In five parallel sessio experts and funders from different fields of personalised medicine discussed and developed solutions for the following topics:
>> read more

ICPerMed@EU-LAC Health Final Conference

On June 15th, Dr. Ulrike Bußhoff, coordinator of ICPerMed Secretariat, represented ICPerMed at the EU-LAC Health Final Conference in Madrid, Spain.
>> read more

About ICPerMed

The International Consortium for Personalised Medicine (ICPerMed) brings together over 30 European and international partners representing ministries, funding agencies and the European Commission (EC). Together, they work on coordinating and fostering research to develop and evaluate personalised medicine approaches.

Despite all efforts, only a limited number of personalised medicine approaches have so far managed the long road from basic biomedical research to clinical application. A lot of investment is made in personalised medicine related research. However, the research efforts in this highly innovative and rapidly changing field are fragmented. Therefore research funders assembled under the umbrella of ICPerMed address this fragmentation challenge on the

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About Us | 100,000 Genomes Project | Taking Part | For Healthcare Professionals | Research | Industry Partnerships | News & Events

Home > The 100,000 Genomes Project

The 100,000 Genomes Project

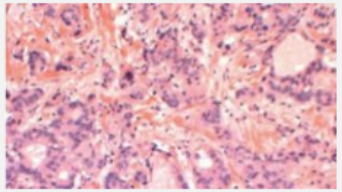
The project will sequence 100,000 genomes from around 70,000 people. Participants are NHS patients with a rare disease, plus their families, and patients with cancer.

The aim is to create a new genomic medicine service for the NHS – transforming the way people are cared for. Patients may be offered a diagnosis where there wasn't one before. In time, there is the potential of new and more effective treatments.

The project will also enable new medical research. Combining genomic sequence data with medical records is a ground-breaking resource. Researchers will study how best to use genomics in healthcare and how best to interpret the data to help patients. The causes, diagnosis and treatment of disease will also be investigated. We also aim to kick-start a UK genomics industry. This is currently the largest national sequencing project of its kind in the world.

Useful links

Cancer
Introduction to cancer in the 100,000 Genomes Project.



https://www.genomicsengland.co.uk/the-100000-genomes-project/

Clinical implementation of PM Impact

- Cancer care
  - Diagnostic evaluation
  - Treatment selection
  - Prognosis
- Monogenic and syndromic conditions
- Therapies
- Reproductive health
  - Cell-free DNA aneuploidy screening
  - Preimplantation genetic diagnosis

Clinical implementation of PM

Ethics

Table 1 Ethical issues associated with the use of companion diagnostics [46]

Issue	Concern
Informed consent	• The process of getting consent from the patient for testing is both lengthy and complex
Data management	• Testing generates data which should be identifiable and integrated into datasets of genomic and health information • Interpreting test data requires skilled professionals who are able to interpret and translate the data to patients
Communication of results	• Translating the results to patients is becoming increasingly difficult, as the number of biomarkers being tested by a single test is constantly increasing • Testing can provide incidental findings and variants of unknown significance, knowledge of which can affect a patient's well-being • Patients have concerns about privacy and the possible disclosure of genetic information. They have concerns about who sees their results during the analysis process and a potential risk of discrimination if such information is known
Cost and equity issues	• The costs for targeted therapies are usually high; drugs and accompanying tests might not always be covered by health insurance, which can limit patients' access to treatment • High costs increase the imbalance in access to new and better treatments as the identification of new biomarkers and treatments continues
Guidelines	• There is a lack of guidelines regarding implementation of testing

Di Paolo A et al. BMC Health Services Research, 2017

Clinical implementation of PM Education

No easy task

- Complex technologies
- In continual evolution
- No guidelines for clinical application (given their newness)

Knowledge asymmetry (geneticist and nongeneticist clinicians)

- Well-intentioned misapplication of tests

nature OUTLOOK

PRECISION MEDICINE

8 September 2016 / Vol 537 / Issue No 7619

The underlying concept of precision medicine, in which health care is individually tailored on the basis of a person's genes, lifestyle and environment, is not new: transfusion patients have been matched with donors according to blood type for more than a century (see page S52). But advances in genetics, and the growing availability of health data, present an opportunity to make precise personalized patient care a clinical reality.

Clinical implementation of PM Education

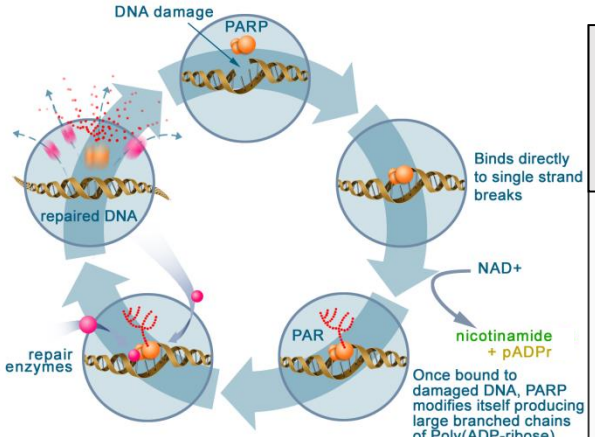
JAMA Insights | GENOMICS AND PRECISION HEALTH

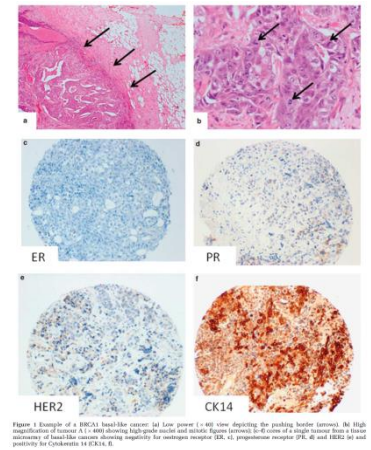
Finding the Rare Pathogenic Variants in a Human Genome

James P. Evans, MD, PhD; Bradford C. Powell, MD, PhD; Jonathan S. Berg, MD, PhD

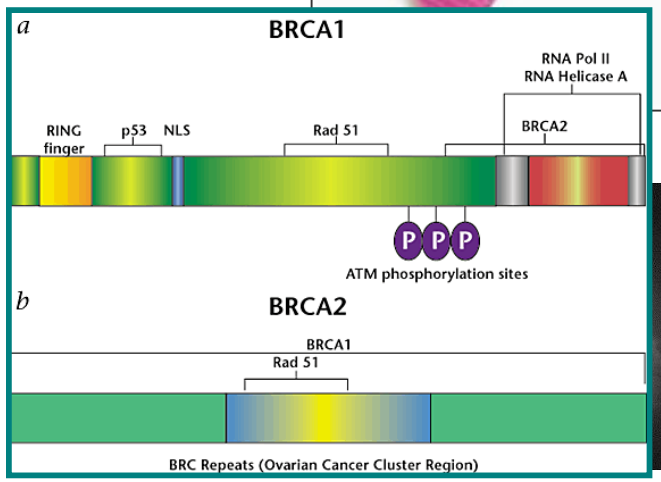
Evans JP et al. JAMA, May 2017

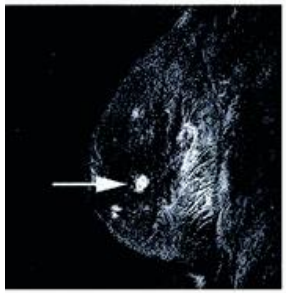
PM should move from treating diseases to managing patients

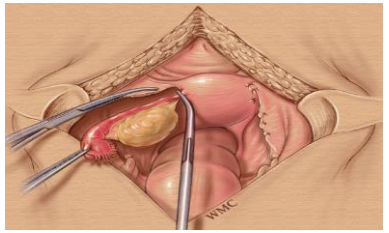


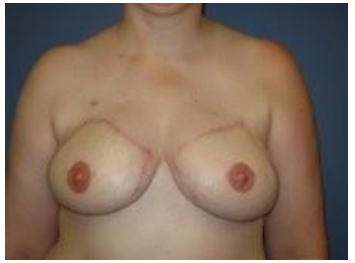


mammaprint®
Breast Cancer Recurrence Signature









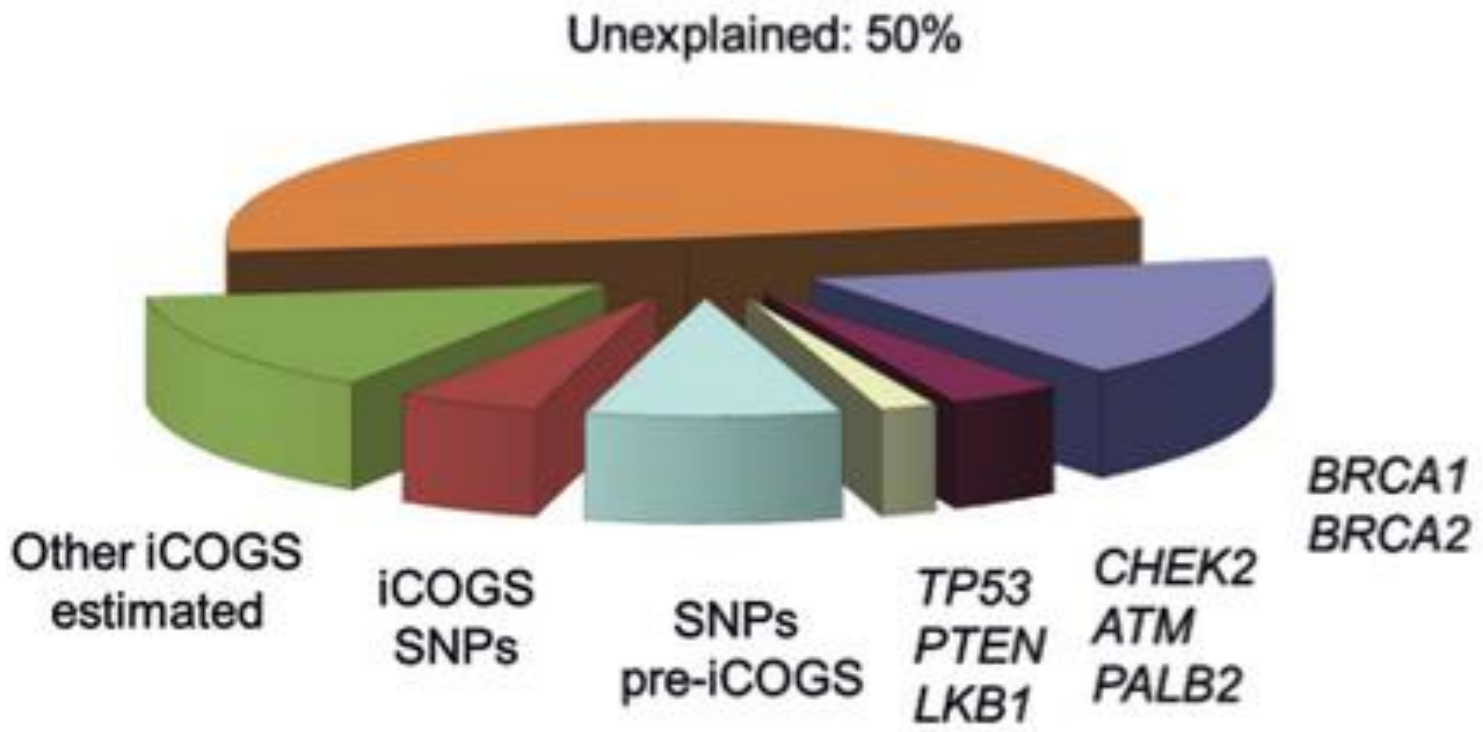
BRCA1
BRCA2
TP53
PTEN
STK11
CDH1

ATM
CHEK2
BRIP1
PALB2

FGFR2
TOX3
MAP3K1
FAM84B/c-MYC
LSP1
NEK10/SLC4A7
COX11
CASP8 (D302H)
TNP1/IGFBP5/IGFBP2/TNS1
NOTCH2/FCGR1B
RAD51L1
MRPS30/FGFR10
ESR1[d]

Slide provided by Dr. Gemma Llort

Inherited susceptibility to Breast Cancer



Common low-penetrance alleles.	**MAF>10%**	**OR<1.5**
Rare moderately penetrant disease-causing variants	**MAF<2%**	**OR≥2.0**
Rare high-penetrance mutations	**MAF≤0.1%**	**OR≥5.0**

http://www.nature.com/icogs/primer

The role of genetic testing panels in breast cancer

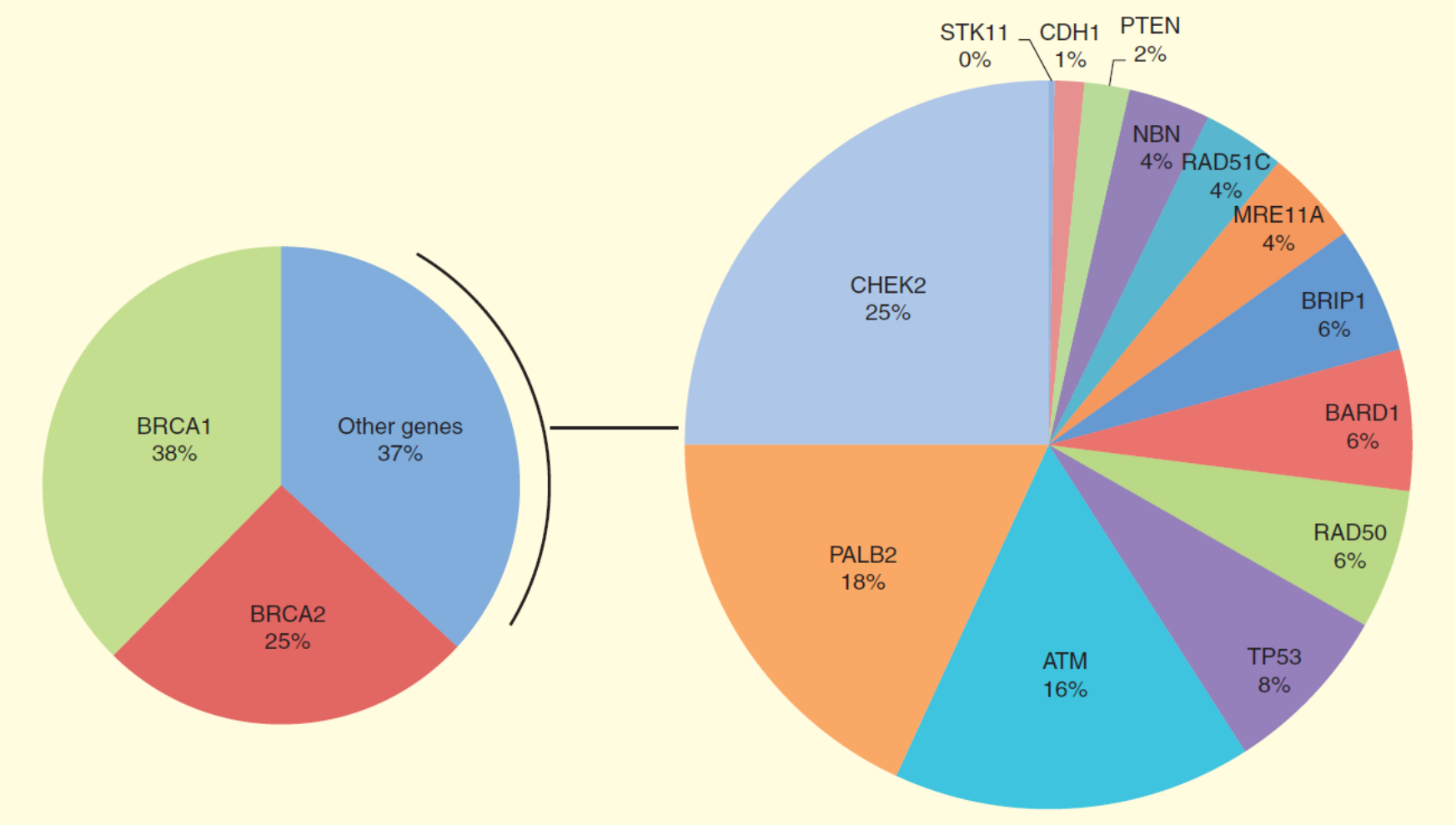


Figure 1. Proportion of pathogenic mutations detected in BRCA1, BRCA2 and 13 other genes included in the gene panel studies.

Lerner-Ellis J et al. Expert Rev Anticancer Ther, 2015

Breast cancer genomic tests

Who´s eligible for the Oncotype DX test?

Recently diagnosed stage I or II invasive BC or DCIS
Cancer is ER-positive
Lymph-node-negative BC
Making decisions about chemotherapy

How does Oncotype DX work?

Looking at these 21 genes, 12 in DCIS, in paraffin-embedded tumoral tissue, can provide specific information on:

Likelihood that the breast cancer will return
Benefits from chemotherapy in early-stage invasive BC
Benefits from radiation therapy in DCIS

mammaprint®
Breast Cancer Recurrence Signature

Who´s eligible for the MammaPrint test?

Invasive stage I or stage II BC
ER-positive or ER-negative
In three or fewer lymph nodes
Smaller than 5 centimeters

How does MammaPrint work?

The MammaPrint test looks at the activity of 70 genes, in fresh tumoral tissue, and then calculates a recurrence score that is either low risk or high risk

The increasing understanding of molecular basis

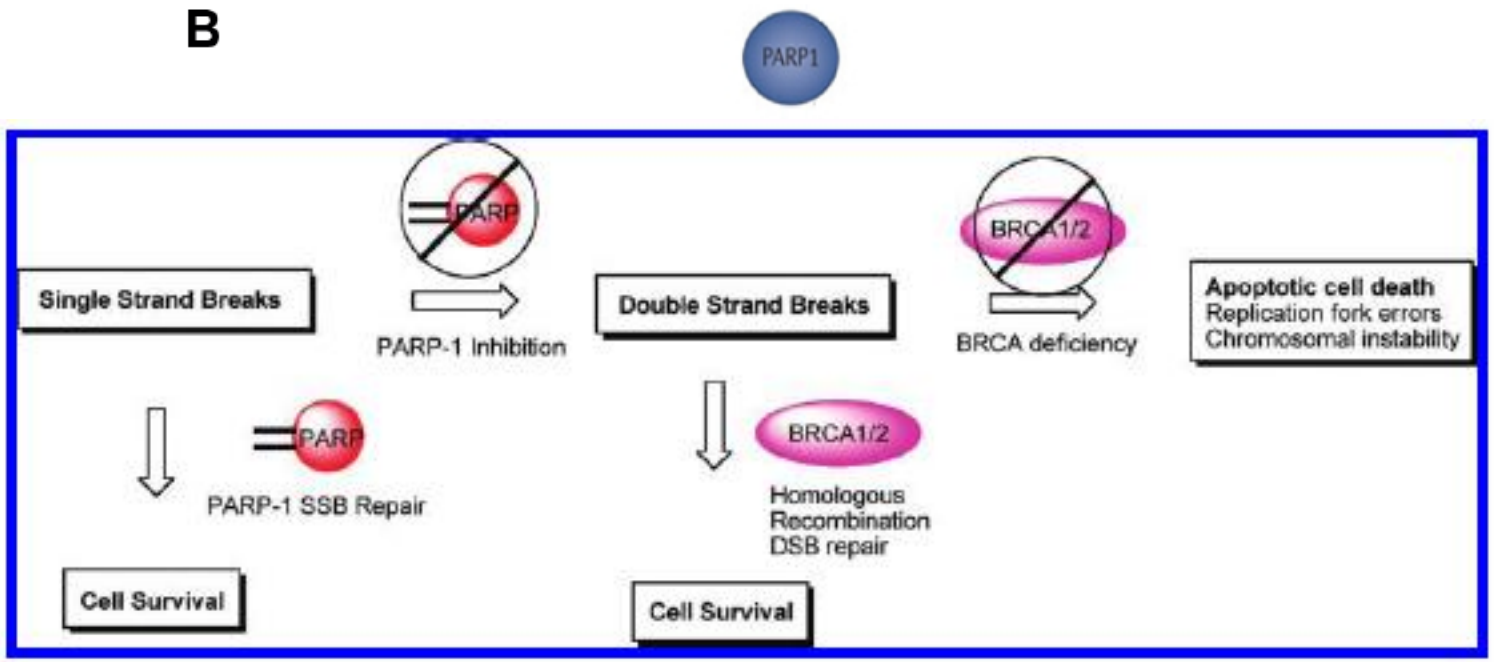


Figure 4. Synthetic lethality of cancer cells.

Figure 1 (**A**) DNA repair pathways; (**B**) PARP senses DNA SSBs and utilizes NAD^+ as a substrate to form PAR, which attach to a range of target proteins including PARP-1 itself and BER proteins. This posttranslational modification is termed PARylation.

Kummar S et al. BMC Medicine, 2012
Benafif & Hall. Onco Targets Ther, 2015

Management and recommendations. Salpingo-ooforectomy

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Oophorectomy on Cancer Incidence and Mortality in Women With a *BRCA1* or *BRCA2* Mutation

Amy P.M. Finch, Jan Lubinski, Pål Møller, Christian F. Singer, Beth Karlan, Leigha Senter, Barry Rosen, Lovise Maehle, Parviz Ghadirian, Cezary Cybulski, Tomasz Huzarski, Andrea Eisen, William D. Foulkes, Charmaine Kim-Sing, Peter Ainsworth, Nadine Tung, Henry T. Lynch, Susan Neuhausen, Kelly A. Metcalfe, Islay Thompson, Joan Murphy, Ping Sun, and Steven A. Narod

5,783 women *BRCA1/2* carriers observed prospectively for an average 5.6 years

Finch APM et al. J Clin Oncol , 2014

Impact of oophorectomy. Cancer incidence ⬇

Table 1. Characteristics of Study Participants by Oophorectomy Status

Variable	No Oophorectomy (n = 2,270) No.	%	Oophorectomy at Baseline (n = 2,123) No.	%	Oophorectomy in Follow-Up (n = 1,390) No.	%	All (N = 5,783) No.	%
Age at study entry, years								
Mean	42.4		50.5		45.0		46.0	
Range	30-86		30-88		30-82		30-88	
Follow-up, years								
Mean	4.59		5.83		6.80		5.58	
Range	0.001-16.8		0.04-16		0.07-16		0.001-16.8	
Age at oophorectomy, years								
Mean	NA		46.8		47.5		47.1	
Range			20-78		26-83		20-83	
Mutation								
BRCA1	1,824	80.4	1,592	75.0	1,057	76.0	4,473	77.4
BRCA2	446	19.6	531	25.0	333	24.0	1,310	22.6
Breast cancer at baseline								
No	1,334	61.8	905	44.9	697	52.8	2,936	53.4
Yes	825	38.2	1,113	55.2	623	47.2	2,561	46.6
Parity								
Nulliparous	514	23.0	239	11.3	183	13.3	936	16.4
Parous	1,718	77.0	1,875	88.7	1,192	86.7	4,785	83.6
Mean	1.7		2.1		2.0		1.9	
Range	0-10		0-9		0-6		0-10	
Oral contraceptive use								
Ever	1,277	57.3	1,425	68.8	882	65.1	3,585	63.4
Never	950	42.7	647	31.2	474	34.9	2,071	36.6
Hormone replacement therapy								
Ever	159	7.4	676	33.3	140	10.6	975	17.7
Never	1,996	92.6	1,354	66.7	1,179	89.3	4,529	82.3
Tamoxifen								
Ever	279	12.3	467	22.0	215	15.5	961	16.6
Never	1,991	87.7	1,655	78.0	1,175	84.5	4,821	83.4
Incident cancer								
No	2,162	95.2	2,100	98.9	1,335	96.0	5,597	96.8
Yes	108	4.8	23	1.1	55	4.0	186	3.2
Clinically detected	108		0		0		108	
Occult	0		0		46		46	
Peritoneal	0		23		9		32	

NOTE. Participants with missing values not included in calculation of proportions.
Abbreviation: NA, not applicable.

Finch APM et al. J Clin Oncol , 2014

Impact of oophorectomy. All-cause mortality ⬇

Table 4. Association Between Oophorectomy and All-Cause Mortality by Age Group, Mutation Status, and History of Breast Cancer

Variable	No. of Patients	*BRCA1*			*BRCA2*			All Patients		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age group at study entry, years										
≤ 40	2,104	0.27	0.15 to 0.48	< .001	0.44	0.17 to 1.09	.08	0.30	0.19 to 0.49	< .001
41-50	1,906	0.23	0.16 to 0.33	< .001	0.29	0.14 to 0.59	< .001	0.24	0.17 to 0.33	< .001
51-60	1,189	0.28	0.19 to 0.43	< .001	0.19	0.08 to 0.43	< .001	0.27	0.18 to 0.38	< .001
≥ 61	584	0.43	0.25 to 0.71	.001	0.89	0.33 to 2.43	.84	0.49	0.31 to 0.76	.002
Total	5,783	0.30	0.24 to 0.38	< .001	0.33	0.22 to 0.50	< .001	0.31	0.26 to 0.38	< .001
Previous breast cancer										
Yes	2,561	0.31	0.24 to 0.39	< .001	0.34	0.22 to 0.52	< .001	0.32	0.26 to 0.39	< .001
No	2,633	0.21	0.12 to 0.37	< .001	0.67	0.08 to 5.35	.70	0.23	0.13 to 0.39	< .001

NOTE. Adjusted by age at study entry, oral contraceptive use (duration), parity (0, 1, 2, 3, or 4+), mutation (*BRCA1* or *BRCA2*), and history of breast cancer at baseline.
Abbreviation: HR, hazard ratio.

Finch APM et al. J Clin Oncol , 2014

Clinical management and recommendations

Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis

Kelly Metcalfe *professor*[1] *adjunct scientist*[2], Shelley Gershman *registered nurse*[1 2], Parviz Ghadirian *professor*[3], Henry T Lynch *professor*[4], Carrie Snyder *registered nurse*[4], Nadine Tung *associate professor*[5], Charmaine Kim-Sing *professor*[6], Andrea Eisen *medical oncologist*[7], William D Foulkes *professor*[8], Barry Rosen *associate professor*[9], Ping Sun *statistician*[2], Steven A Narod *professor*[2]

1) 390 *BRCA1/2* mutation carriers with BC and unilateral or bilateral (181) mastectomy, were followed for up to 20y from diagnosis

2) 79 women died of BC in the follow up period: 18 in the bilateral mastectomy group and 61 in the unilateral mastectomy.

3) At 20 y the survival rate for women who had mastectomy of the contralateral breast was 88% and for those did not was 66%

4) Multivariable analysis, controlling for age of diagnosis, year of diagnosis, treatment, and other prognostic features, contralateral mastectomy was associated with 48% reduction in death from BC

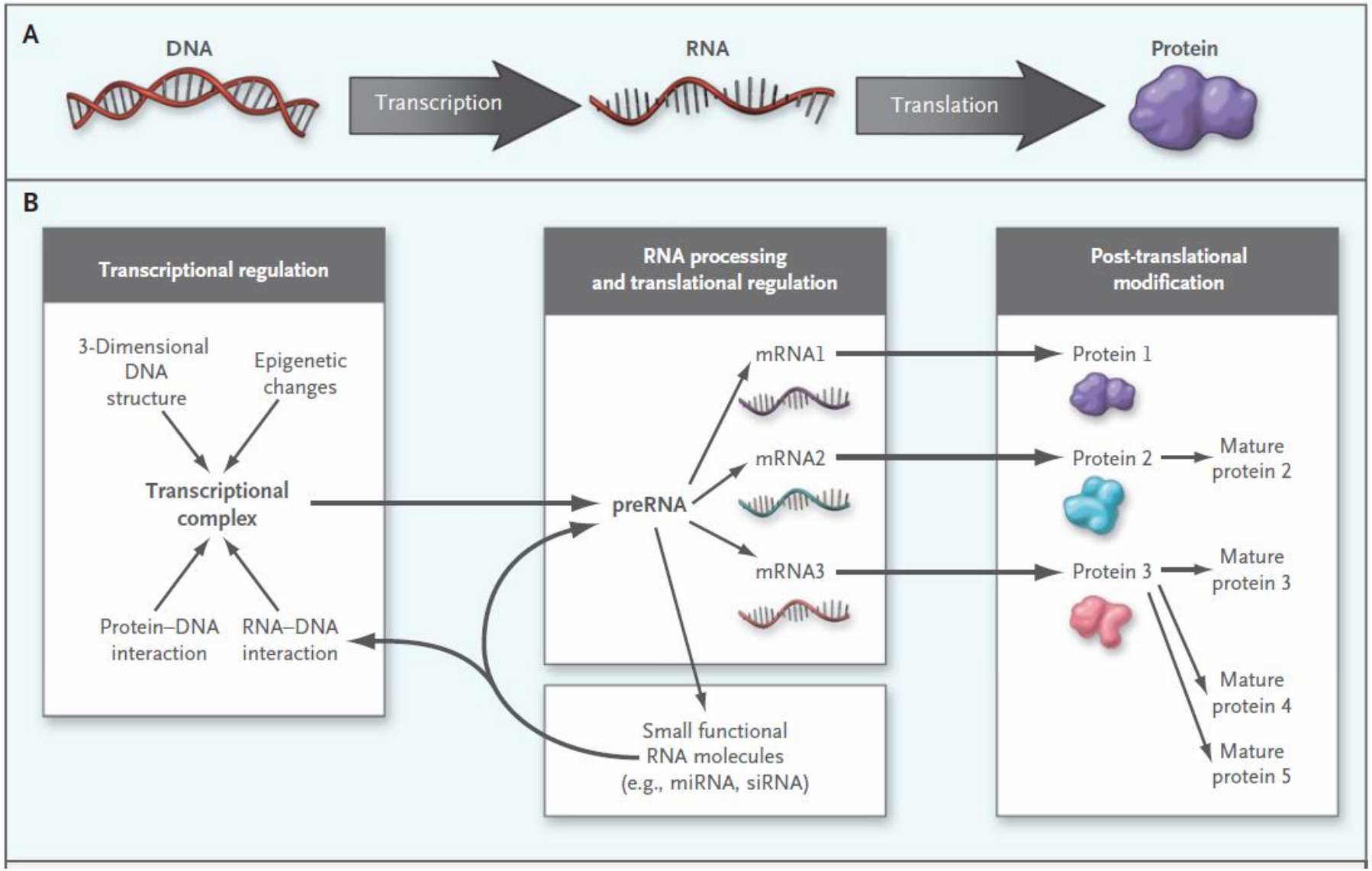
Metcalfe K et al. BMJ, 2014

Screening recommendations in BRCA carriers (SEOM)

	Age	Evidence and recommendation
Women		
Breast self awareness	Starting at age 18 years	**IIA**
Clinical breast exam every 6–12 months	Starting at age 25 years	**IIA**
Annual breast MRI	25–70 years	**IIA**
Annual mammogram	30–35 to 75 years	**IIA**
Transvaginal ultrasound and Ca 12.5 every 6–12 months	30 years	**IIC**
Men		
Breast self awareness	Starting at age 35 years	**IIIC**
Annual clinical breast exam	Starting at age 35 years	**IIIC**
Basal mammogram	40 years (individualised)	**IIIC**
Annual Prostate Cancer screening	Starting at age 40 years	**IIIB**
Men and women		
Pancreatic and melanoma	Consider individualised screening based on cancers in the family	**IIIC**
Colorectal cancer screening, especially in BRCA1	Starting at 40 years or younger if family history	**IIB**

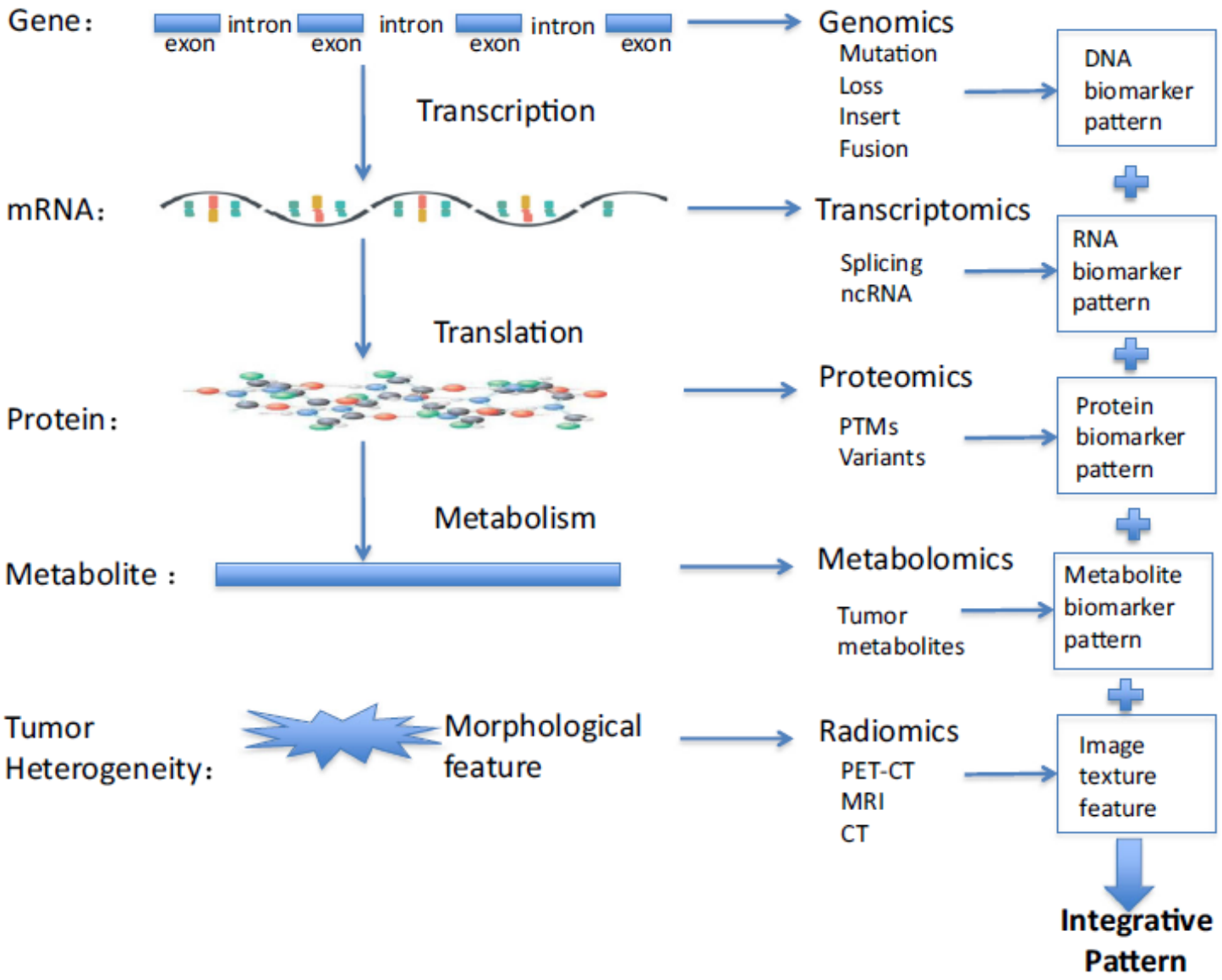
Llort G et al. Clin Transl Oncol, 2015

Defining the gene and its regulation



Feero WG & Guttmacher AE. N Engl J Med, 2011

The development of techniques offers promise to find more biomarker pattern



Cheng T & Zhan X. EPMA Journal, 2017

Genomic variation. There is no "normal" human genome sequence.

Glossary

- Humans are very similar at the DNA sequence level; about 99.6% of base pairs are identical from person to person.

- Given the size of the genome (approximately 6 billion bp in every nucleated non–germ-line cell), there is substantial latitude for individual genetic variation, since the difference between any two people is about 24 million bp.

Allele: One of two or more versions of a genetic sequence at a particular location in the genome.

Mutation: A change in a DNA sequence. Germ-line mutations occur in the eggs and sperm and can be passed on to offspring, whereas somatic mutations occur in body cells and are not passed on.

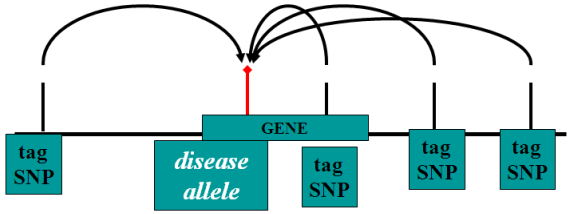
Single-nucleotide polymorphism (SNP): A single-nucleotide variation in a genetic sequence; a common form of variation in the human genome (frequency greater tan 1%).

HapMap: The nickname of the International HapMap (short for "haplotype map") Project, an international venture that seeks to map variations in human DNA sequences to facilitate the discovery of genetic variants associated with health. The HapMap describes common patterns of genetic variation among people.

Feero WG & Guttmacher AE. N Engl J Med, 2011

GWAS

Genome-wide approach

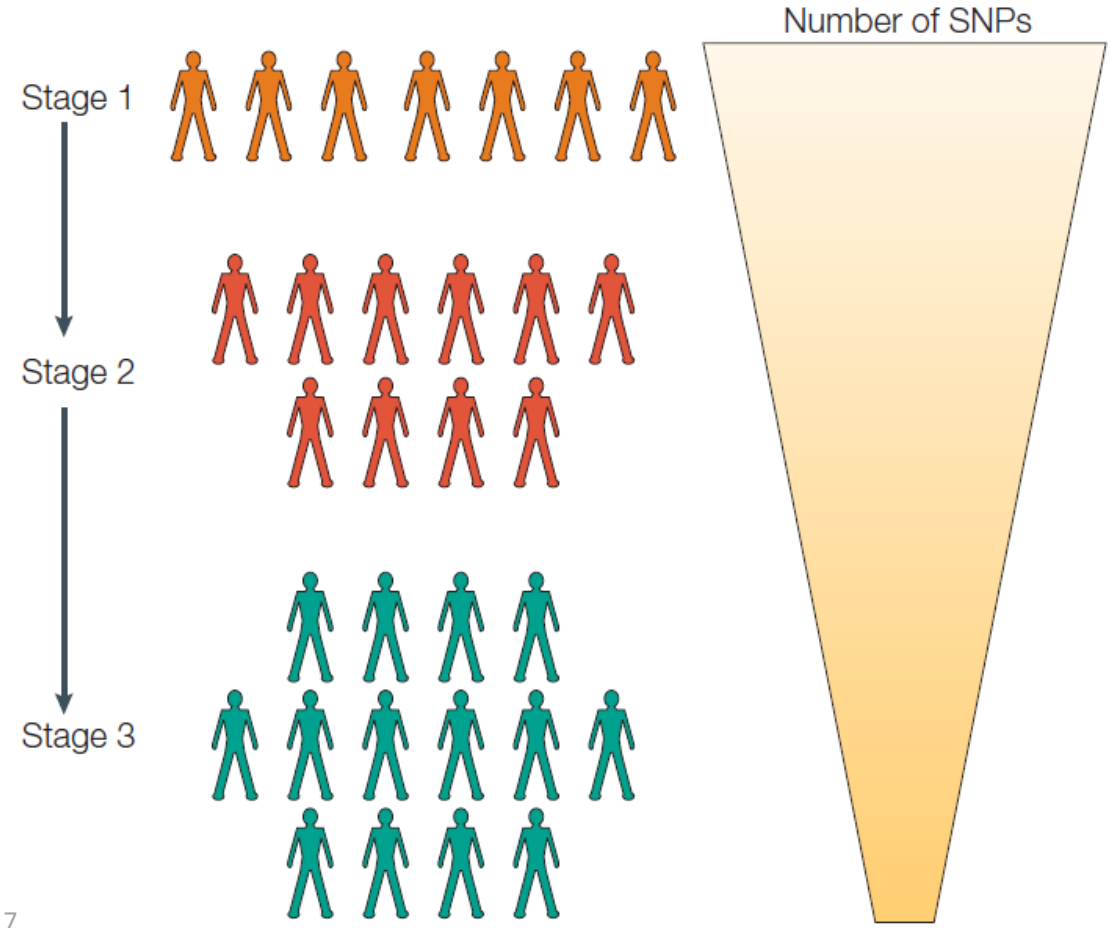


No SNPs selection

Chromosomal regions, no genes

Many positive cases by chance

Replication in independent cohort



Genotype full set of SNPs in relatively small population at liberal *p* value

Screen second, larger population at more stringent *p* value

Optional third stage for increased stringency

Multistage approach

Hirschhorn JN & Daly MJ. Nature Rev, 2005

GWAS

nature genetics

Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2

Marker (chromosome, position)	Alleles[a]	Stage (cases/controls)	MAF[b]	Per-allele OR (95% CI)[c]	Heterozygote OR (95% CI)[d]	Homozygote OR (95% CI)[e]	*P* trend
rs4973768		Stage 1 (388/355)	0.46	1.33 (1.07–1.64)	1.45 (1.01–2.07)	1.76 (1.15–2.68)	0.0087
(3p24, 27391017)	C/T	Stage 2 (3,951/3,870)	0.47	1.06 (0.99–1.03)	0.99 (0.89–1.10)	1.13 (0.99–1.28)	0.081
		Stage 3 (3,872/3,925)	0.48	1.13 (1.06–1.20)	1.03 (0.93–1.15)	1.27 (1.12–1.44)	0.00025
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		Combined					4.1×10^{-23}
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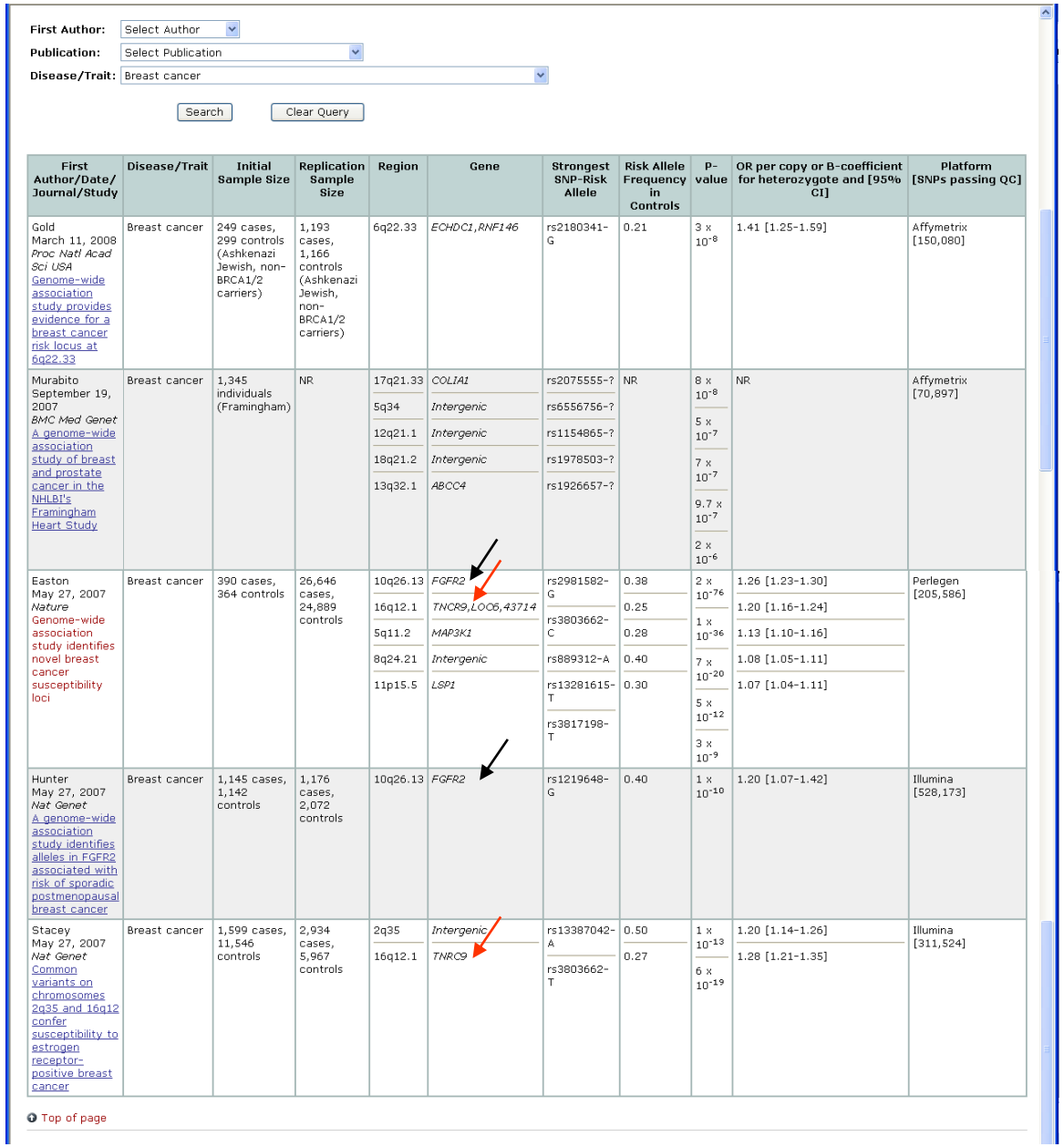
		Stage 4 (30,470/33,302)	0.27 (0.08)	0.95 (0.92–0.97)	0.96 (0.92–0.99)	0.89 (0.83–0.95)	0.00010
		Combined					1.4×10^{-8}

Ahmed S et al. Nat Genet, 2009

GWAS in breast cancer



First Author: Select Author
Publication: Select Publication
Disease/Trait: Breast cancer

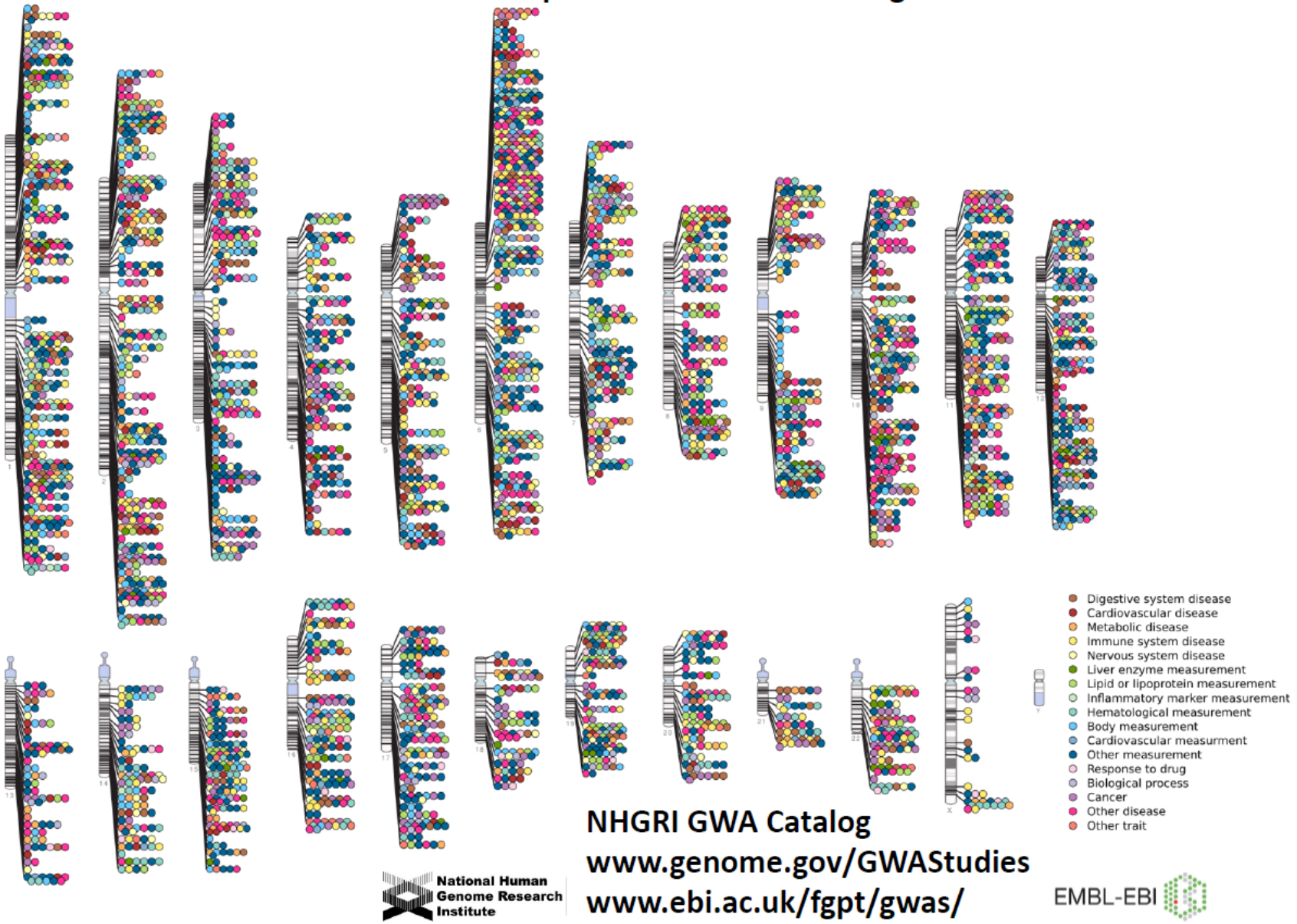
Search | Clear Query

First Author/Date/ Journal/Study	Disease/Trait	Initial Sample Size	Replication Sample Size	Region	Gene	Strongest SNP-Risk Allele	Risk Allele Frequency in Controls	P-value	OR per copy or B-coefficient for heterozygote and [95% CI]	Platform [SNPs passing QC]
Gold March 11, 2008 *Proc Natl Acad Sci USA* Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33	Breast cancer	249 cases, 299 controls (Ashkenazi Jewish, non-BRCA1/2 carriers)	1,193 cases, 1,166 controls (Ashkenazi Jewish, non-BRCA1/2 carriers)	6q22.33	*ECHDC1,RNF146*	rs2180341-G	0.21	3×10^{-8}	1.41 [1.25-1.59]	Affymetrix [150,080]
Murabito September 19, 2007 *BMC Med Genet* A genome-wide association study of breast and prostate cancer in the NHLBI's Framingham Heart Study	Breast cancer	1,345 individuals (Framingham)	NR	17q21.33 5q34 12q21.1 18q21.2 13q32.1	*COL1A1* *Intergenic* *Intergenic* *Intergenic* *ABCC4*	rs2075555-? rs6556756-? rs1154865-? rs1978503-? rs1926657-?	NR	8×10^{-8} 5×10^{-7} 7×10^{-7} 9.7×10^{-7} 2×10^{-6}	NR	Affymetrix [70,897]
Easton May 27, 2007 *Nature* Genome-wide association study identifies novel breast cancer susceptibility loci	Breast cancer	390 cases, 364 controls	26,646 cases, 24,889 controls	10q26.13 16q12.1 5q11.2 8q24.21 11p15.5	*FGFR2* *TNCR9,LOC6,43714* *MAP3K1* *Intergenic* *LSP1*	rs2981582-G rs3803662-C rs889312-A rs13281615-T rs3817198-T	0.38 0.25 0.28 0.40 0.30	2×10^{-76} 1×10^{-36} 7×10^{-20} 5×10^{-12} 3×10^{-9}	1.26 [1.23-1.30] 1.20 [1.16-1.24] 1.13 [1.10-1.16] 1.08 [1.05-1.11] 1.07 [1.04-1.11]	Perlegen [205,586]
Hunter May 27, 2007 *Nat Genet* A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer	Breast cancer	1,145 cases, 1,142 controls	1,176 cases, 2,072 controls	10q26.13	*FGFR2*	rs1219648-G	0.40	1×10^{-10}	1.20 [1.07-1.42]	Illumina [528,173]
Stacey May 27, 2007 *Nat Genet* Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer	Breast cancer	1,599 cases, 11,546 controls	2,934 cases, 5,967 controls	2q35 16q12.1	*Intergenic* *TNRC9*	rs13387042-A rs3803662-T	0.50 0.27	1×10^{-13} 6×10^{-19}	1.20 [1.14-1.26] 1.28 [1.21-1.35]	Illumina [311,524]

Top of page

Published Genome-Wide Associations through 12/2013

Published GWA at $p \leq 5X10^{-8}$ for 17 trait categories

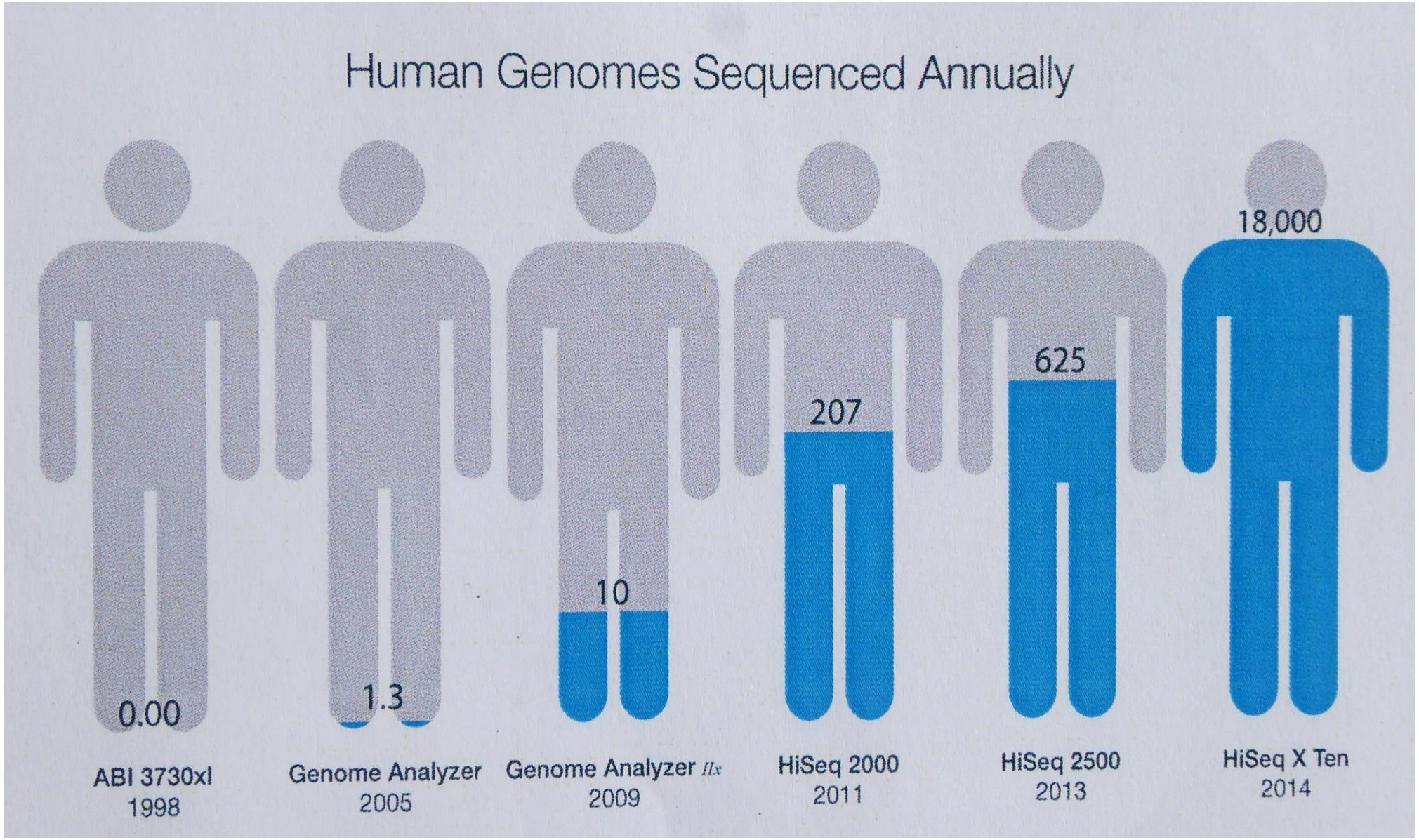


https://www.genome.gov/gwastudies/

APPLICATIONS OF NEXT-GENERATION SEQUENCING

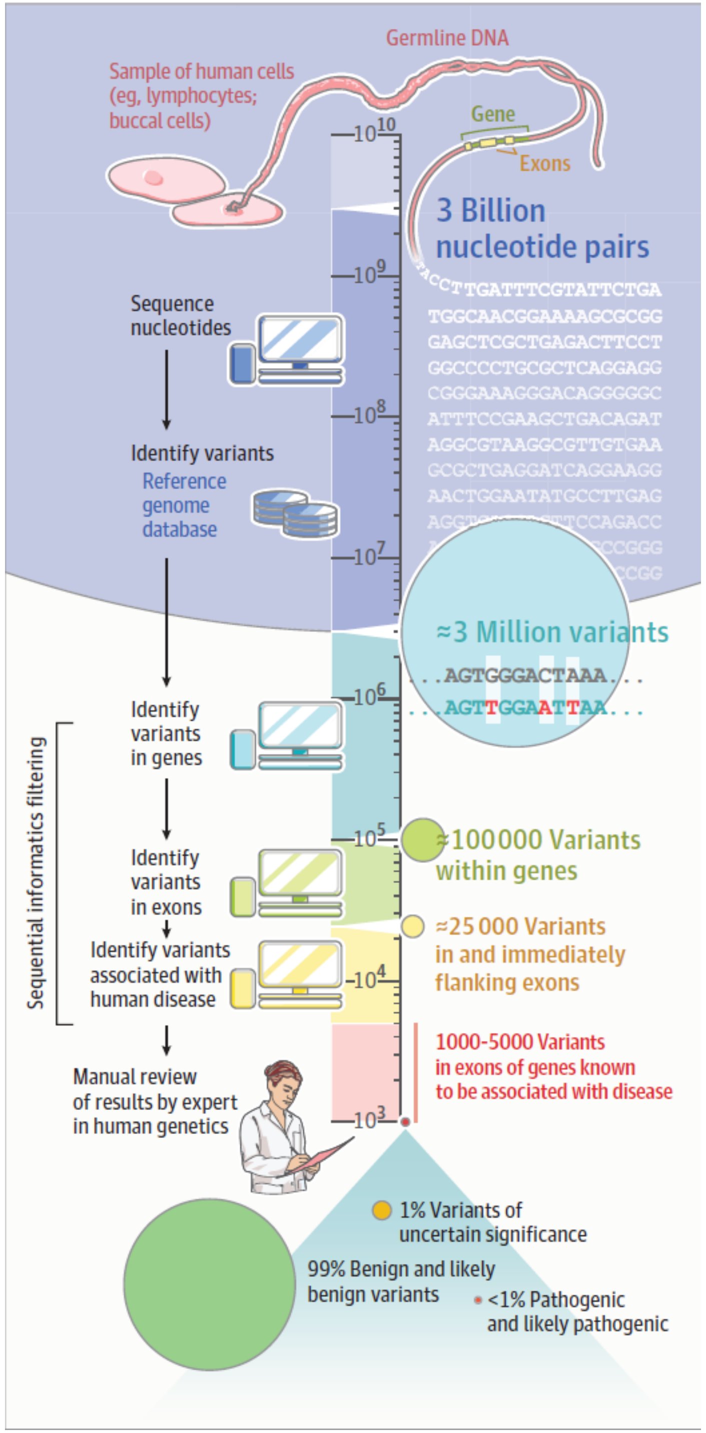
Coming of age: ten years of next-generation sequencing technologies

Sara Goodwin[1], John D. McPherson[2] and W. Richard McCombie[1]



https://www.illumina.com/science/technology/next-generation-sequencing.html

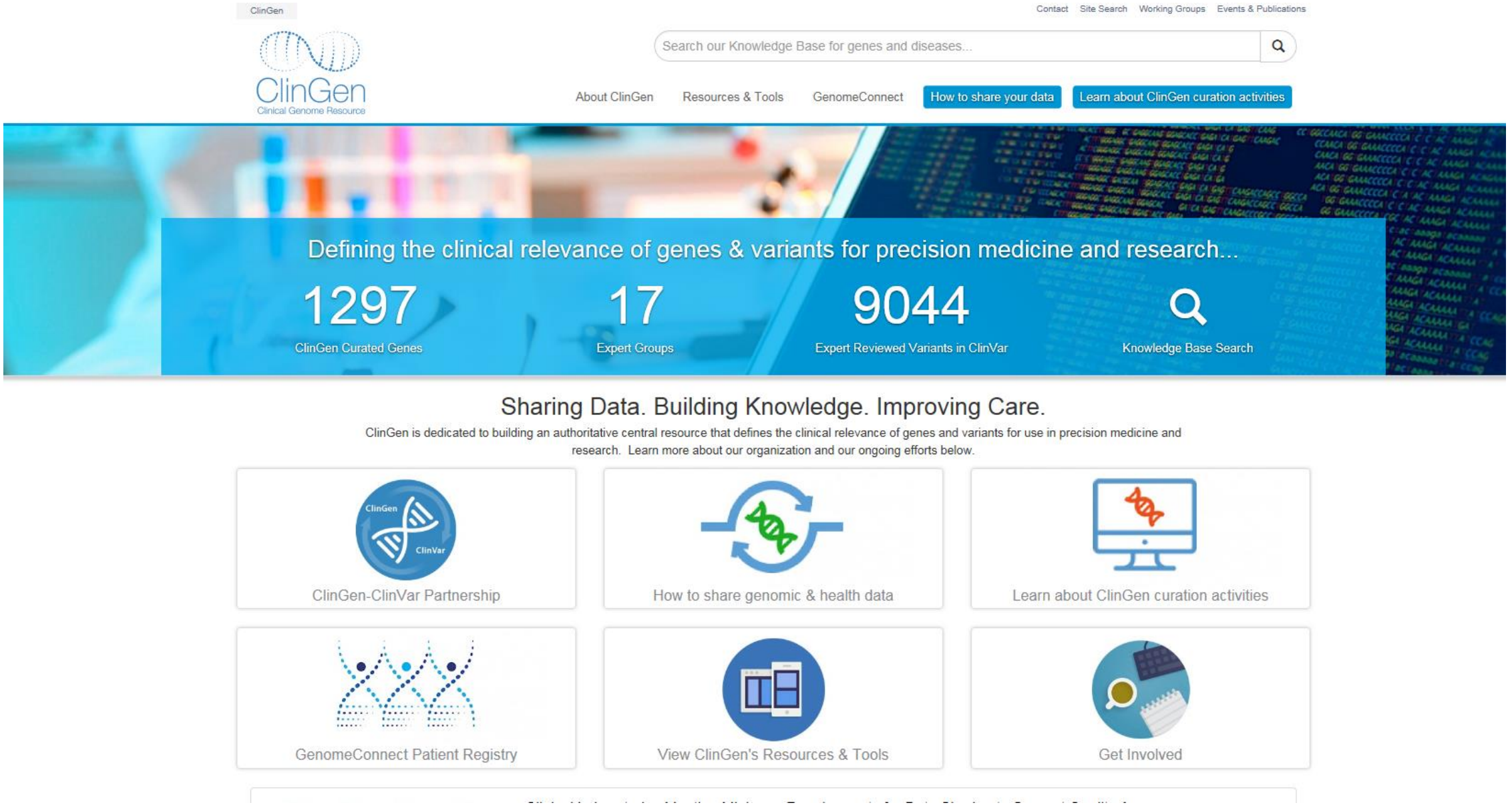
WGS



- A genome sequence is not a single test.
- It represents millions of tests in which each nucleotide of a genome is queried and variants departing from a reference sequence are reported.
- Genomic information rarely results in a yes or no answer about disease state, but rather a probabilistic estimate of risk.

- The chance of an individual manifesting a genetic disease depends on 2 factors:
  . the certainty with which a variant is associated with disease, and
  . the penetrance of the condition
- Lack of knowledge of either factor impairs the predictive value of genetic information, resulting in false positives (variants interpreted as being likely pathogenic but that actually are benign) and overdiagnoses (pathogenic variants that do not lead to disease due to incomplete penetrance).

Evans JP et al. JAMA, 2017



https://www.clinicalgenome.org/

Identification of new Cancer Predisposition Genes by NGS

nature COMMUNICATIONS

ARTICLE

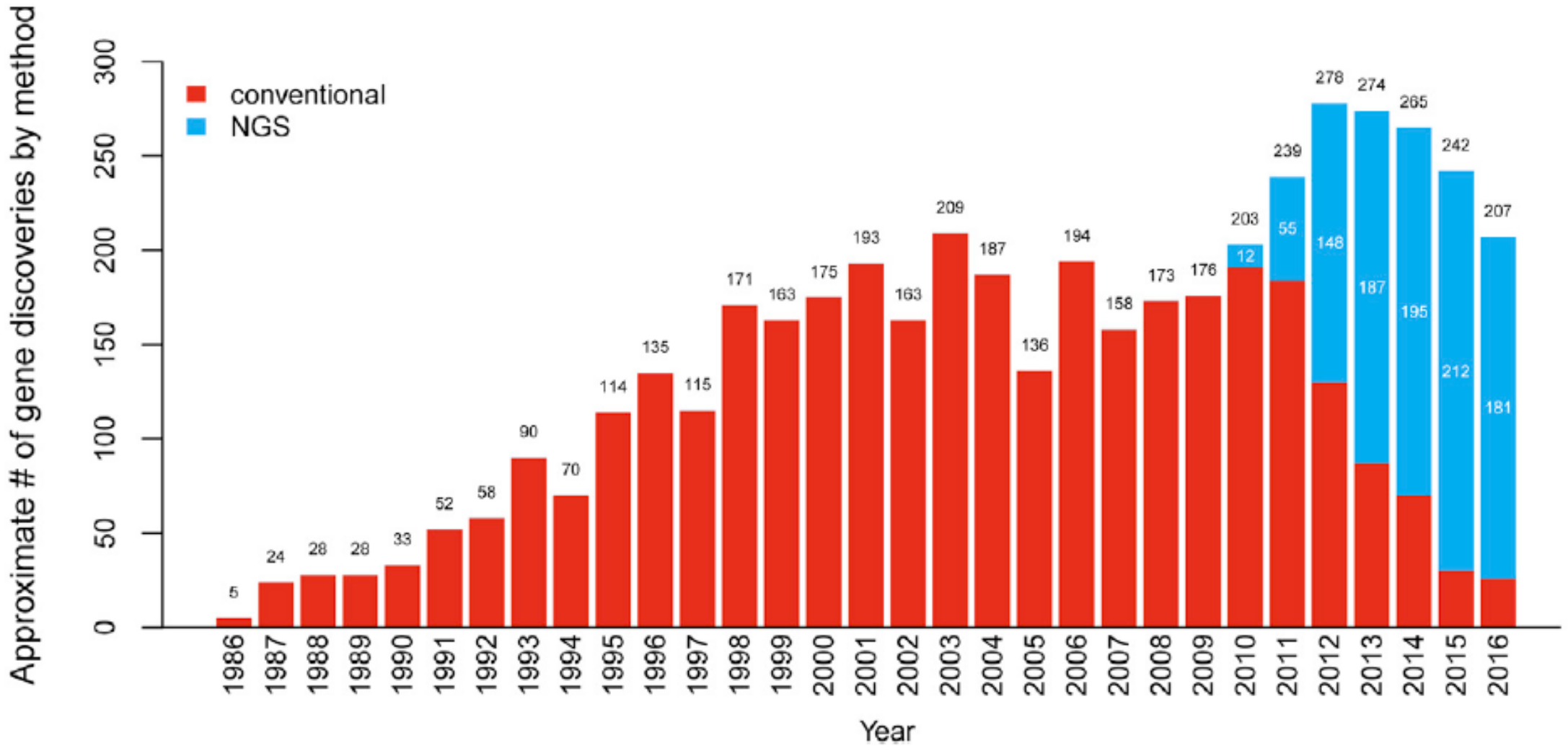
Received 6 Apr 2015 | Accepted 14 Aug 2015 | Published 25 Sep 2015

DOI: 10.1038/ncomms9383 OPEN

A mutation in the *POT1* gene is responsible for cardiac angiosarcoma in *TP53*-negative Li–Fraumeni-like families

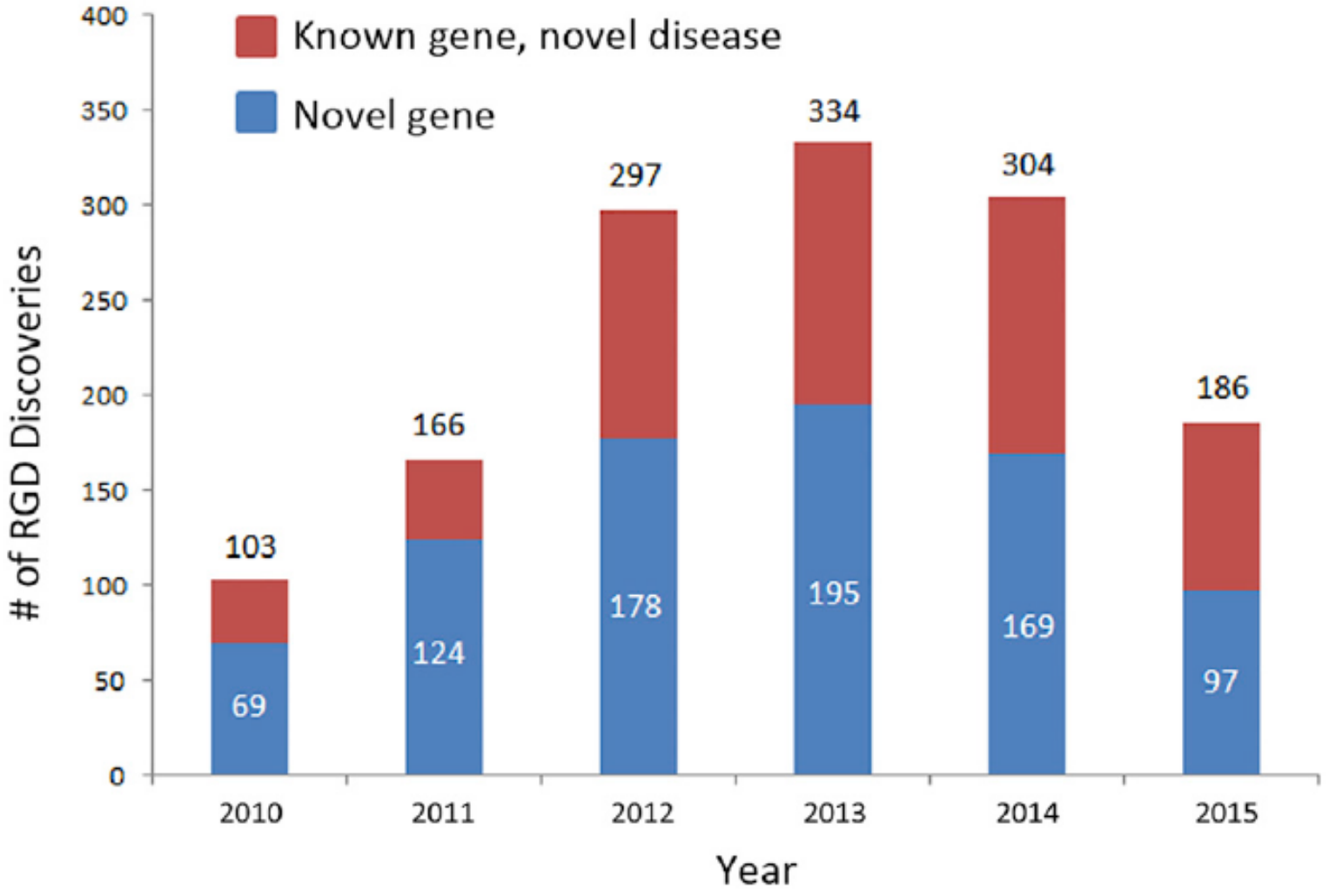
Oriol Calvete[1,2,*], Paula Martinez[3,*], Pablo Garcia-Pavia[4,5], Carlos Benitez-Buelga[1], Beatriz Paumard-Hernández[1], Victoria Fernandez[1], Fernando Dominguez[4], Clara Salas[6], Nuria Romero-Laorden[7], Jesus Garcia-Donas[7], Jaime Carrillo[8], Rosario Perona[2,8], Juan Carlos Triviño[9], Raquel Andrés[10], Juana María Cano[11], Bárbara Rivera[12,†], Luis Alonso-Pulpon[4], Fernando Setien[13], Manel Esteller[13,14,15], Sandra Rodriguez-Perales[16], Gaelle Bougeard[17], Tierry Frebourg[17], Miguel Urioste[2,12], Maria A. Blasco[3,**] & Javier Benítez[1,2,**]

Approximate Number of Gene Discoveries Made by WES and WGS versus Conventional Approaches since 2010 according to OMIM Data



Boycott KM et al. Am J Hum Genet, 2017
Chong JX et al. Am J Hum Genet, 2015

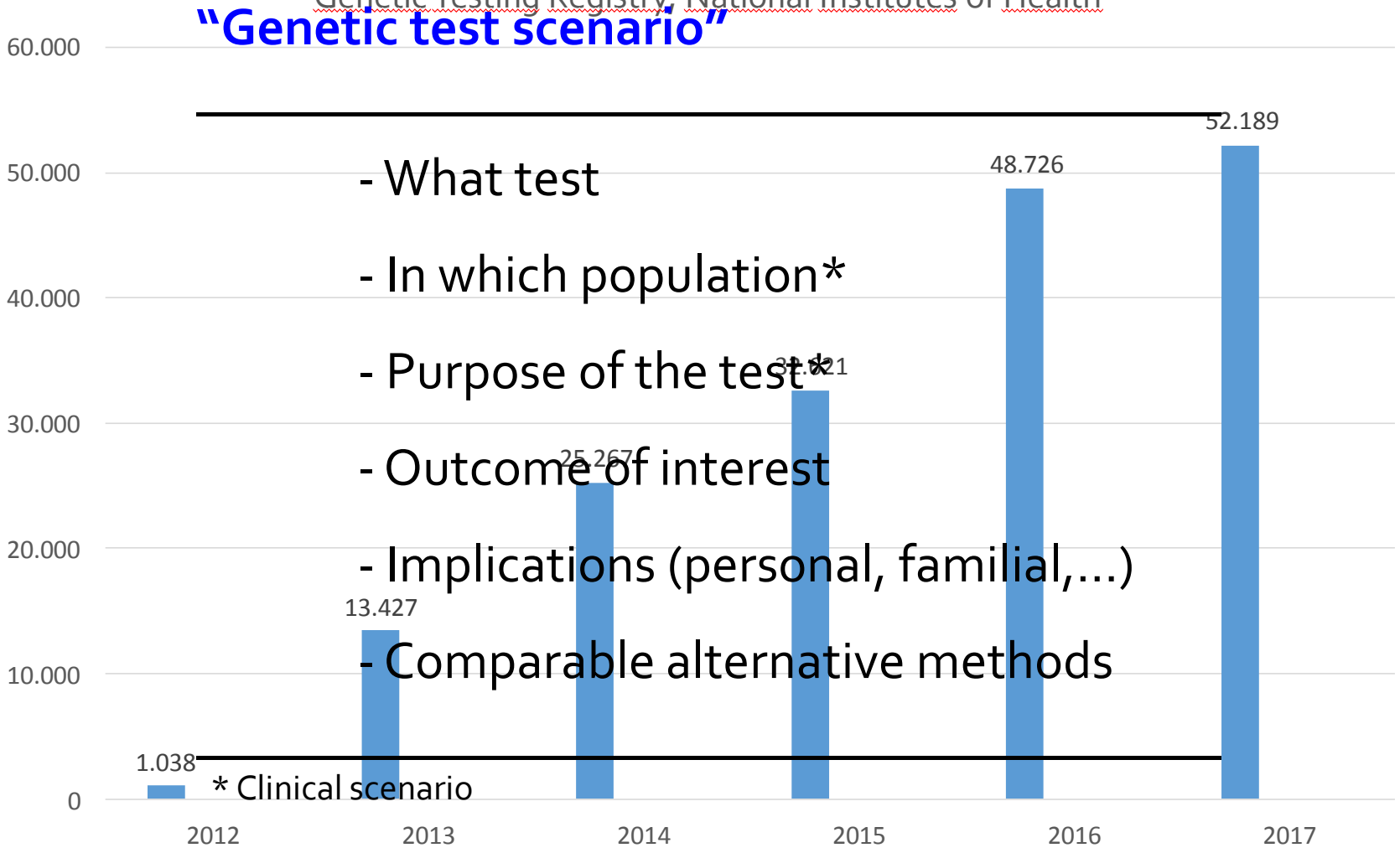
Approximate Number of Novel Gene-Phenotype Discoveries from 2010 to 2015 according to Orphanet Data



Boycott KM et al. Am J Hum Genet, 2017

Number of genetic tests available for research and clinical practice

Genetic Testing Registry, National Institutes of Health



"Genetic test scenario"

- What test
- In which population*
- Purpose of the test*
- Outcome of interest
- Implications (personal, familial,…)
- Comparable alternative methods

* Clinical scenario

Two clinical axiomas

1.- “Don’t order a test unless you know what to do with the result”

2.- “When you order 20 tests, each with 95% specificity, you are likely to get at least one false positive result”

Direct-to-Consumer (DTC) Medical Testing

- Growing medical marketplace offers (low-value) medical testing directly to consumers

  $15 million/2010 $130 million/2015 $350 million/2020

- Tests are ordered online without a physician order.

- Consumers purchase tests without a prescription/examination and regardless medical history

- Companies offer tests to the public without any reference to evidence-based guidelines

- Advertisements appeal to fears of contracting common disorders

- Tests have a low/negative value for a large segment of the consuming public

- Relative lack of regulation compared with the health care industry

- The FDA recently approved 10 DTC tests despite their low clinical value

Rockwell KL. JAMA, June 2017

DTC. Cascade of additional downstream interventions

- Consumers cannot obtain advice about their results

- Patient anxiety over results, patient selfmisdiagnosis

- They will need to see their physicians for guidance

- Physicians that never order such testing are not familiar with responding to the results

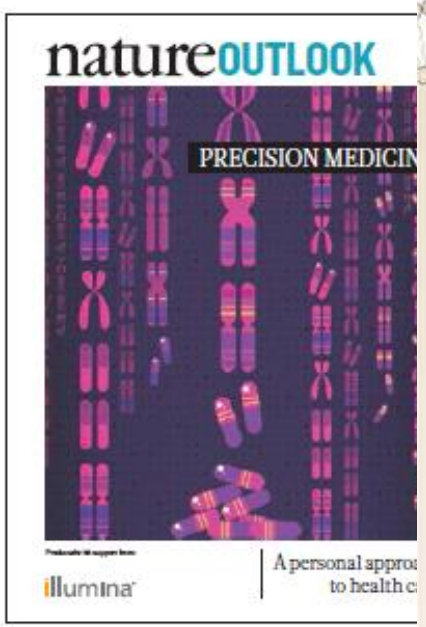
- Risks of downstream interventions based on low-value testing

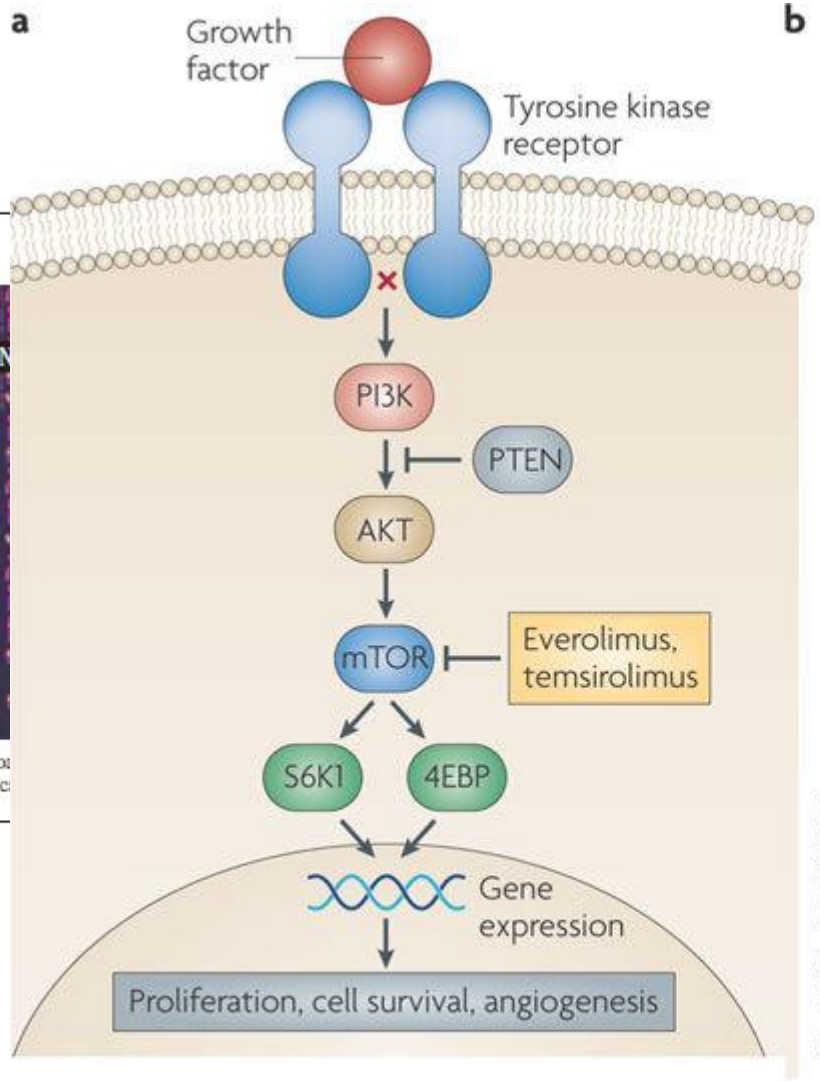
Refer to a specialist, repeat testing, order additional tests, etc

- There are also important health care system implications related to cost.

Rockwell KL. JAMA, June 2017

Precision oncology remains a hypothesis in need of verification





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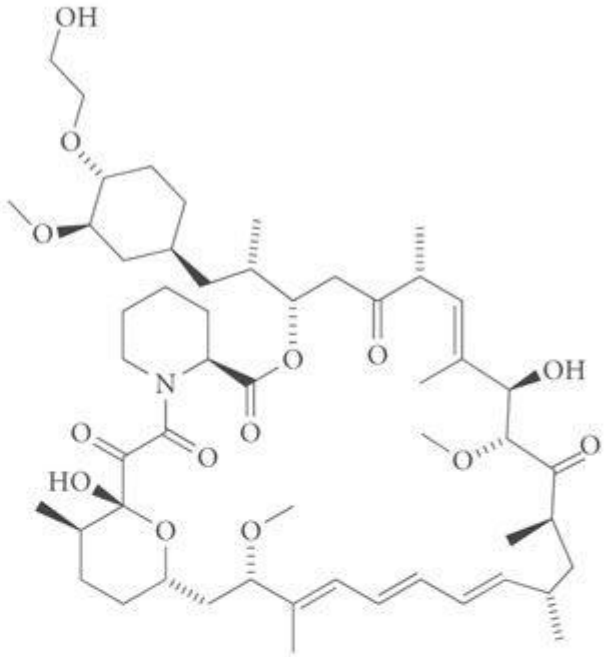


Everolimus

(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*)-1,18- dihydroxy-12-{(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone; $C_{53}H_{83}NO_{14}$; M_r = 958.2

illusion

perhaps it never

Nature Reviews | Drug Discovery

Few patients benefit from precision oncology.

Centre	Population	Method	Results (% patient/drug match)
MD Anderson	2,600 advanced ca.	50-genes panel	6.4
US National Cancer Inst.	795 relapsed tumors	tumor seq	2

Meric-Bernstam F et al. J Clin Oncol, 2015
http://ecog-acrin.org/nci-match-eay131/interim-analysis

But being assigned such a therapy is not proof of benefit.

Treatment based on biological markers

Estimation:

Precision Medicine (Oncology) will benefit around **1.5%** of patients with relapsed and refractory solid tumors

---

Respond at all	30%
Median progression-free survival	5.7 months

Schwaederle M et al. JAMA Oncol, 2016

The ultimate judge of a therapeutic strategy is the randomized controlled trial .

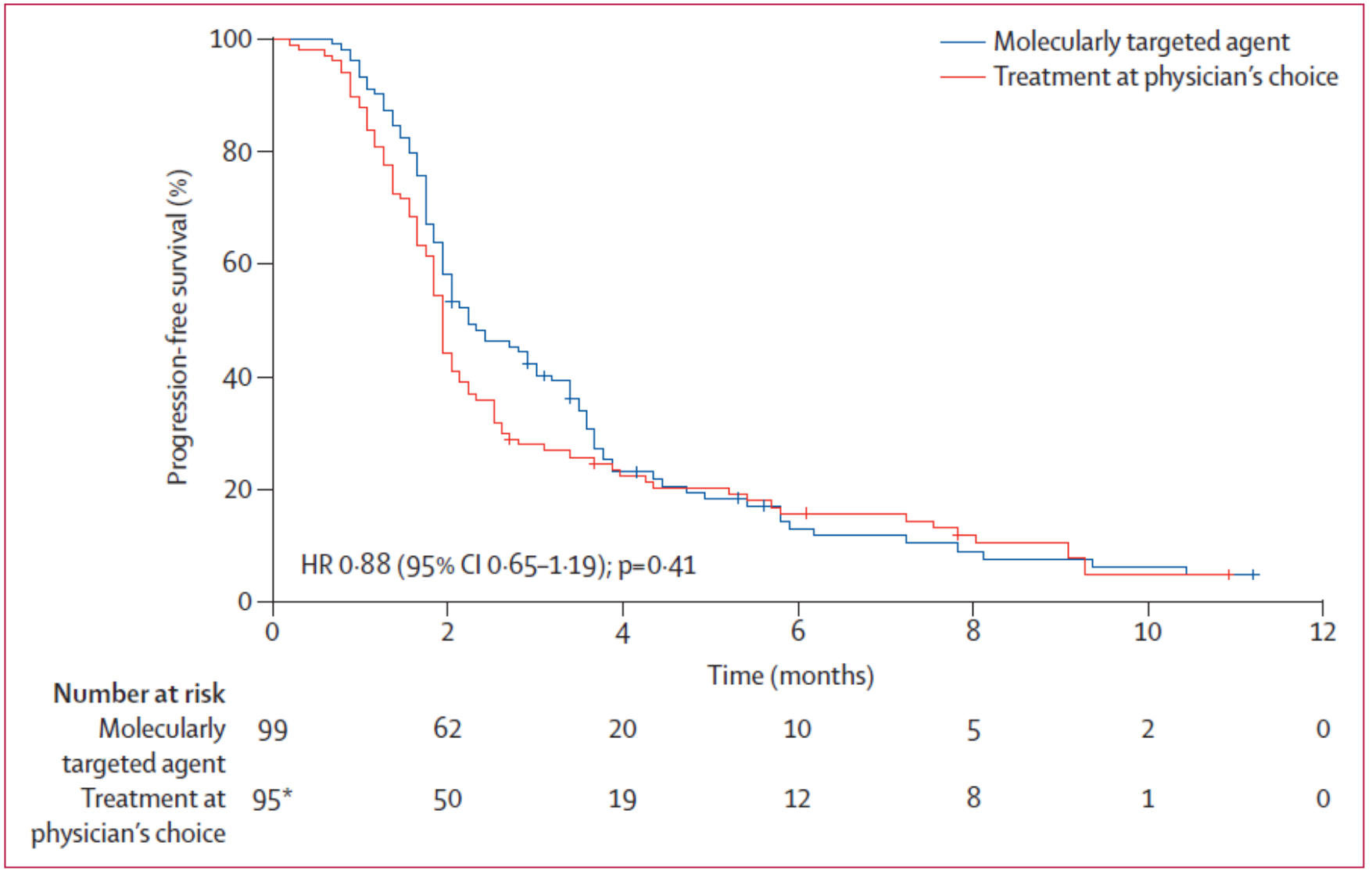


Figure 3: Progression-free survival

SHIVA trial

Median progression-free survival was 2.3 months in the experimental group versus 2.0 months in the control group.

Le Torneau C et al. Lancet Oncol, 2015

Will Precision Medicine (PM) improve Population Health (PH)?

PM can improve PH

PM might not Improve PH

1.- Stratification of populations into risk groups for multiple chronic diseases could provide more efficient and effective prevention and treatment strategies

1.- Disease pathogenesis of common diseases is extraordinarily complex

2.- Genetically targeted approach to health has demonstrated a PH benefit (newborn screening, hereditary cancers)

2.- The identification of good predictors is unlikely in common diseases different to cancer

3.- High-risk individuals rarely change their behavior to avoid the disease

3.- PM technologies and big data are leading to a new era of precision public health that goes beyond personalized treatment of individuals affected by disease.

a) Applying emerging methods and technologies for measuring disease, pathogens, exposures, behaviors, and susceptibility in populations

b) Developing policies and targeted implementation programs to improve health

Khoury MJ & Galea S. JAMA, 2016

Will Precision Medicine improve Population Health?

Research

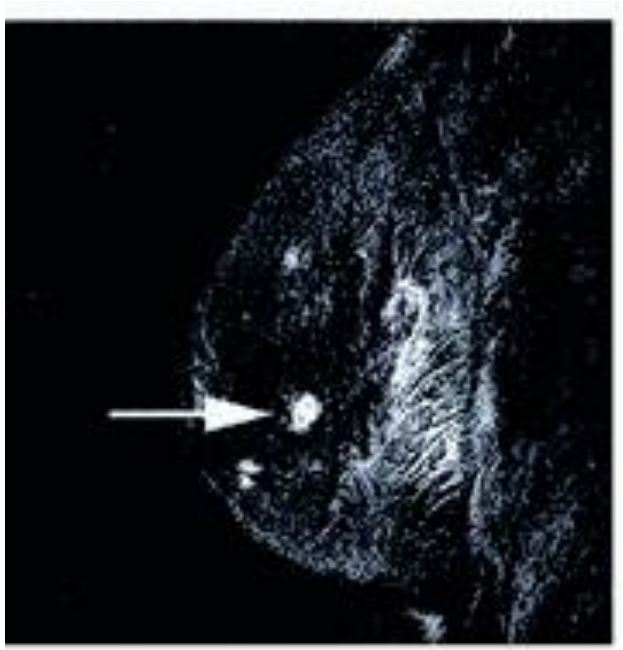
JAMA Oncology | Original Investigation

Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States

Paige Maas, PhD; Myrto Barrdahl, PhD; Amit D. Joshi, PhD; Paul L. Auer, PhD; Mia M. Gaudet, PhD; Roger L. Milne, PhD; Fredrick R. Schumacher, PhD;

Maas P et al. JAMA Oncology, 2016

Precision Medicine & Public Health

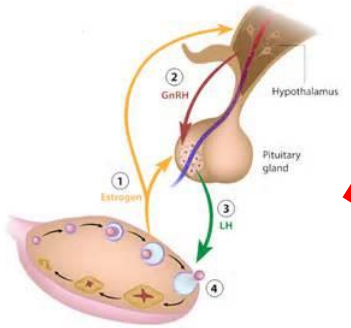


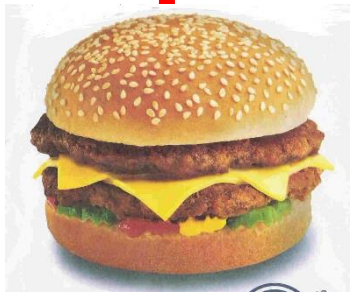
TIPO DE CÁNCER	Nº CASOS	95 % CI	CR	95 % CI	ASIRw	95 % CI	ASIRe	95 % CI
Mama	27.747	24.027-31.957	117,5	101,7-135,3	65,2	56,1-75,5	88,3	76,1-102,1

TIPO DE CÁNCER	0-39	0-49	0-59	0-69	0-79	0-84
Mama	0,44	1,86	3,82	5,80	7,88	8,99

SEOM. Las cifras del cáncer en España, 2017

Geneticists and epidemiologists are aware that cancer strikes neither capriciously nor randomly





Maas P et al. JAMA Oncology, 2016

GWAS

nature genetics

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		Stage 4 (30,470/33,302)	0.27 (0.08)	0.95 (0.92–0.97)	0.96 (0.92–0.99)	0.89 (0.83–0.95)	0.00010
		Combined					1.4×10^{-8}

Ahmed S et al. Nat Genet, 2009

Breast Cancer Risk from Modifiable and Nonmodifiable Risk Factors

Nonmodificable factors

- 17,171 cases and 19,862 controls

From The Breast and Prostate Cancer Cohort Consortium

- To develop a empirical model for predicting absolute risk of breast cancer.

- The model includes modificable and nonmodificable risk components

Table 3. Comparison of Empirically Estimated and Theoretically derived Odds Ratios for deciles of PRS-24

Polygenic risk score (PRS)	Estimated Odds Ratios	
	Empirical	Theoretical Model
PGRS Decile 1	1	1
PGRS Decile 2	1·19	1·21
PGRS Decile 3	1·32	1·42
PGRS Decile 4	1·43	1·48
PGRS Decile 5	1·54	1·59
PGRS Decile 6	1·65	1·76
PGRS Decile 7	1·80	1·92
PGRS Decile 8	2·07	2·04
PGRS Decile 9	2·26	2·32
PGRS Decile 10	2·79	2·88
Family History	1·40	1·37

Modificable factors

Family history

Age at first birth

Parity

Age of menarche

Height

Menopausal status

Body mass index

Menopausal hormone therapy

Alcohol consumption

Smoking status

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Breast Cancer Risk from Modifiable and Nonmodifiable Risk Factors

Table 1. Total Number of At-Risk Subjects and Incident Cases Expected at Different Risk Levels for Every 100 000 Women With Assessed Risk

	Model					
	PRS-92 Only		Questionnaire-Based Risk Factors Only		PRS-92 and Risk Factors	
Risk Level	Total Subjects, No.	Cases, No.	Total Subjects, No.	Cases, No.	Total Subjects, No.	Cases, No.
Moderate risk: RR = 2-3[a]	2691	688	306	74	4116	1076
High risk: RR>3[a]	109	40	0	0	649	181
10-y risk at 40 is > average 10-y risk at 50[b]	9113	295	6531	194	16 134	564
10-y risk at 50 is < average 10-y risk at 40[c]	27 018	380	11 231	184	32 037	425

Abbreviations: PRS, polygenic risk score; PRS-92, all 92 known breast cancer SNPs; RR, relative risk; SNP, single nucleotide polymorphisms.

[a] The reference is 11.3%, the average risk in women ages 30 to 80 years.

[b] The average 10-y risk at age 50 years is 2.6%.

[c] The average 10-y risk at age 40 years is 1.8%.

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Breast Cancer Risk from Modifiable and Nonmodifiable Risk Factors

Figure 3. Distribution of Absolute Lifetime Risk Associated With Modifiable Risk Factors Stratified by Deciles of Nonmodifiable Risk for White Women in the United States

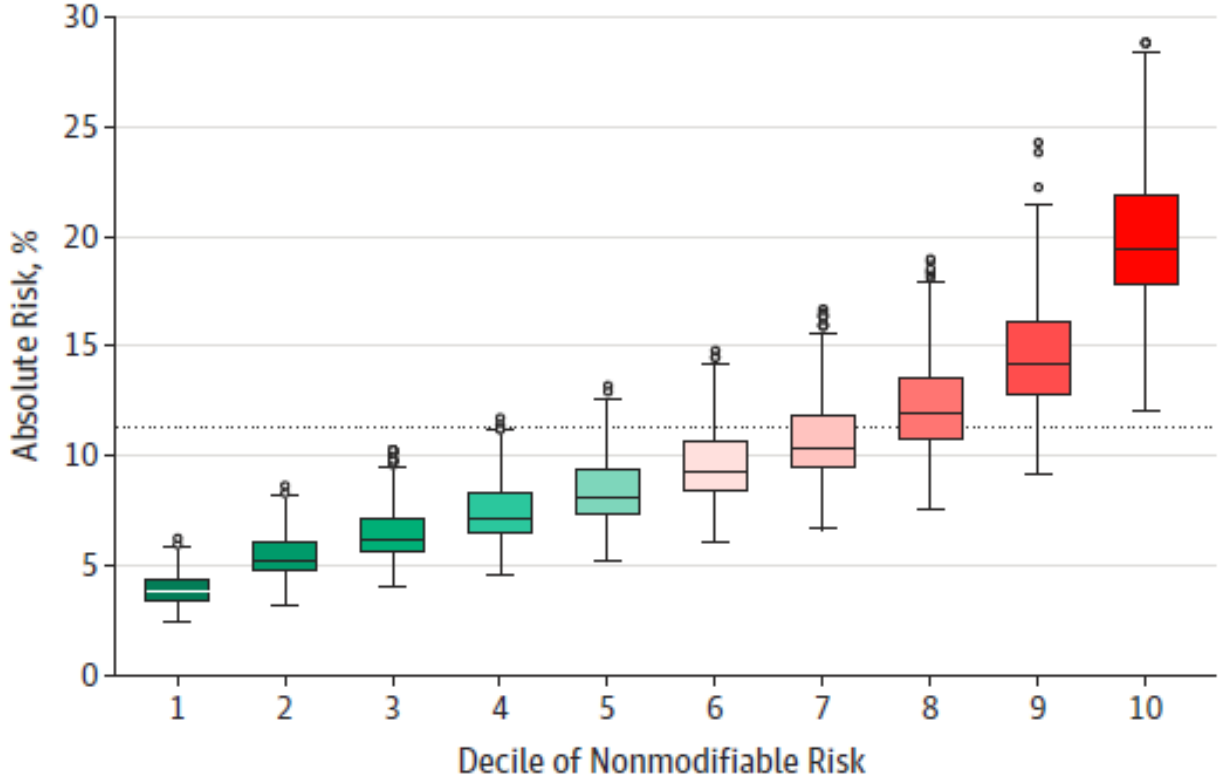

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Table 2. Estimates of Proportion of Breast Cancer Cases Preventable by Reduction of Modifiable Risk in Different Strata of the Population Defined by Nonmodifiable Risk Factors[a]

	Proportion of Breast Cancer, %									
	Alcohol		MHT		BMI[b]		Smoking		All 4 Modifiable Risk Factors Simultaneously[c]	
Nonmodifiable Risk Groups	P	T	P	T	P	T	P	T	P	T
Decile										
1	4.00	0.36	4.60	0.31	4.80	0.57	4.10	0.12	4.40	1.28
2	5.50	0.49	5.80	0.38	6.30	0.76	5.70	0.17	5.90	1.70
3	6.60	0.59	7.00	0.47	7.20	0.87	6.80	0.21	7.00	2.01
4	7.70	0.69	8.30	0.55	8.10	0.98	7.90	0.24	8.00	2.31
5	8.60	0.77	8.80	0.58	9.10	1.09	8.70	0.27	8.80	2.55
6	9.90	0.89	9.50	0.63	10.10	1.22	9.60	0.30	9.80	2.84
7	11.10	1.00	11.10	0.74	10.90	1.32	10.80	0.33	11.00	3.18
8	12.40	1.11	12.00	0.80	12.10	1.46	12.50	0.38	12.20	3.53
9	14.70	1.32	14.30	0.95	13.80	1.66	15.20	0.47	14.30	4.14
10	19.7	1.78	18.50	1.23	17.50	2.11	18.80	0.58	18.50	5.35
PAR[d]	-	9.01	-	6.64	-	12.05	-	3.08	-	28.90

Abbreviations: BMI, body mass index; MHT, menopausal hormone therapy; P, total number of preventable breast cancers; PAR, population-attributable risk; T, total number of breast cancers.

[a] The proportions for each stratum are shown relative to the total number of breast cancers (%T) and total number of preventable breast cancers (%P) that are expected to arise in the whole population.

[b] BMI is calculated as weight in kilograms divided by height in meters squared.

[c] The modifiable risk factors are body mass index, MHT use, alcohol use, and smoking.

[d] Estimate of population-attributable risk due to modifiable factors (individually and simultaneously). PAR is given by column sum of T and %P = (%T/PAR) × 100 .

Maas P et al. JAMA Oncology, 2016

Breast Cancer Risk from Modifiable and Nonmodifiable Risk Factors

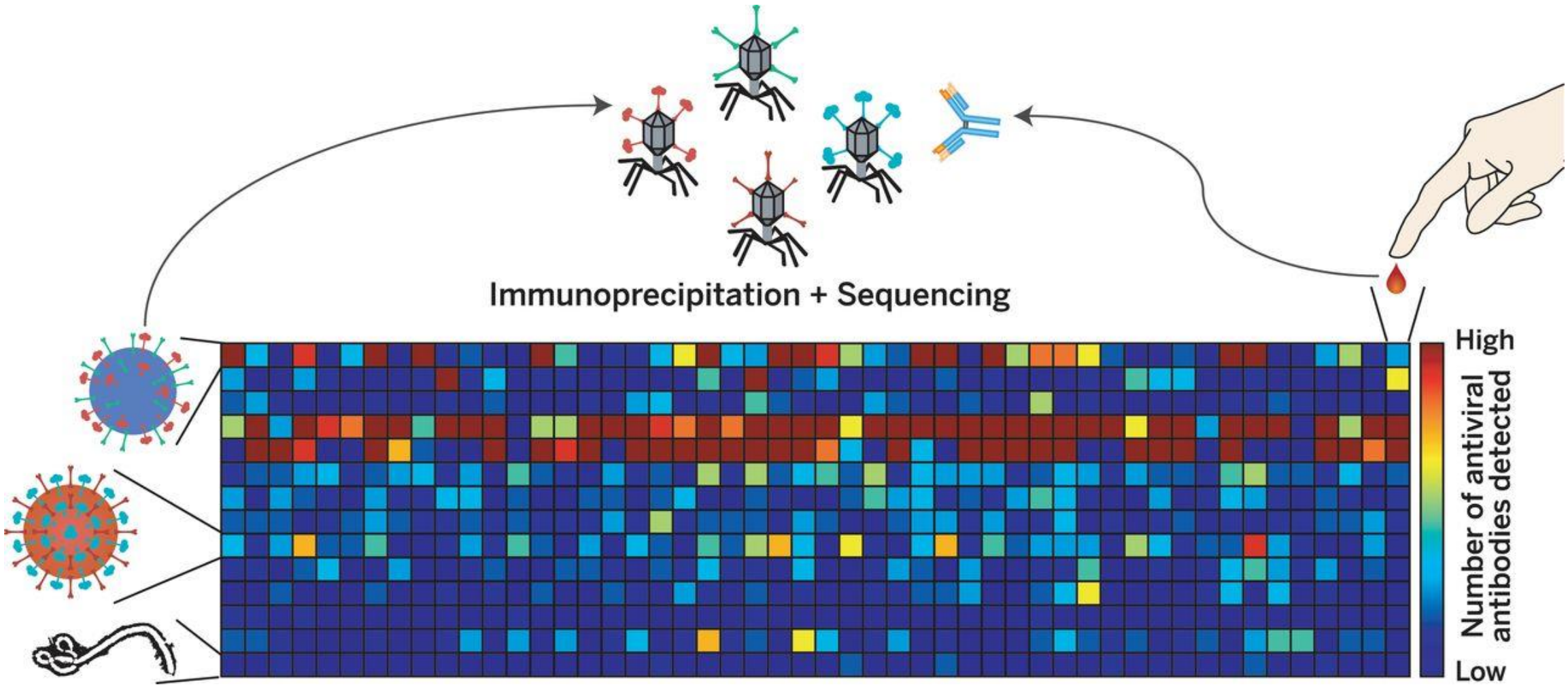
Conclusions

These results illustrate the potential value of risk stratification to improve breast cancer prevention, particularly to aid decisions on risk factor modification at the individual level.

The effect of such models for improving the cost-benefit ratio of population-based prevention programs will depend on the implementation cost of risk assessment.

Maas P et al. JAMA Oncology, 2016

Precision Medicine & Public Health



Xu GJ et al. Science, 2015
Kish LJ & Topol EJ. Nat Biotech, 2015

Colorectal cancer (CRC)

- Third most common cancer
- It is of paramount importance to elucitate CT resistence in CRC patients

Second leading cause of cancer-related death

- Cancer chemoresistence results from a complex interplay between gene regulation and environment

Chemotherapy (CT): 5-fluorouracil, Capecitabine, Oxaliplatin

The majority of patients are initially responsive

- Microbiota is linked to CRC initiation and progression via affecting metabolism and inflammation.

Patients with tumor recurrence due to drug resistance have por prognosis

Microbiota

- Complex communities of microorganisms live on and in the human body, and variations in the composition and function of these communities are increasingly linked to various conditions and diseases, mainly related with immunoregulation (allergies, autoimmunity, inflammatory bowel disease)

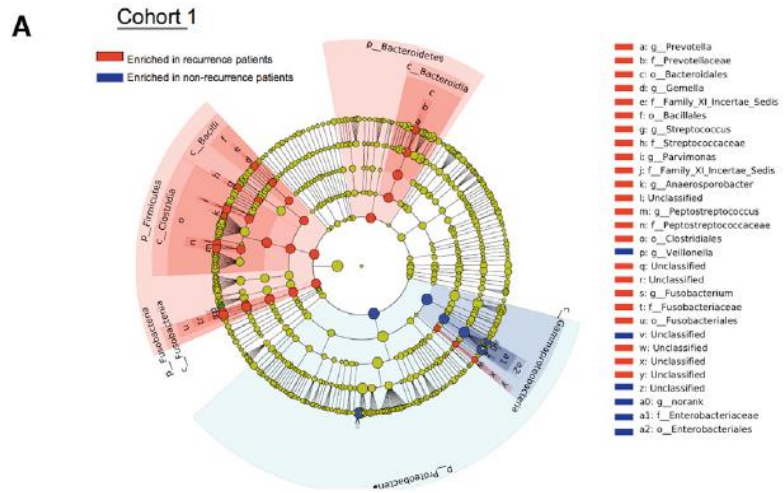
- Although it is not known if microbiome changes are causative or consequential in most pathophysiologies, they might provide biomarkers for disease detection or management

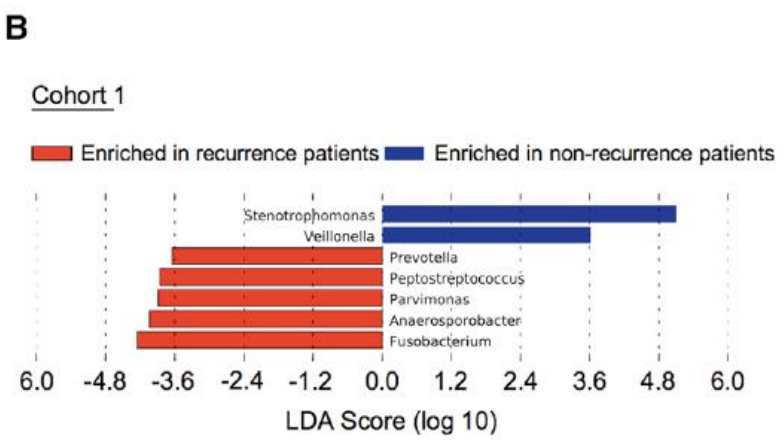
- Microbiome analysis is likely to become a routine component of secondary health care and is emerging as a modifiable environmental risk factor in multifactorial diseases that could be targeted by novel therapeutics

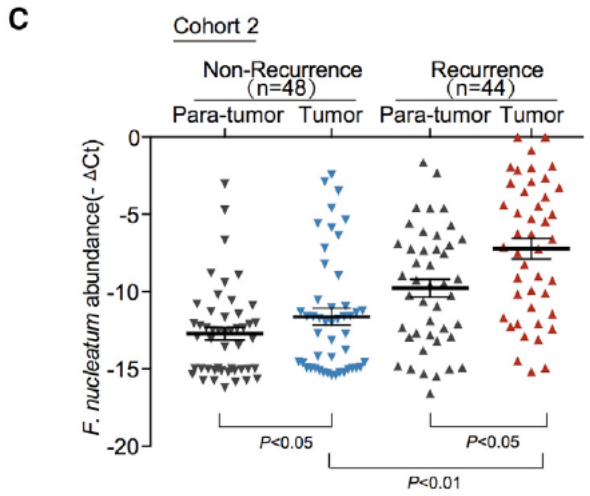
- Technology advancements are leading to a range of powerful methods for microbiome analysis becoming available and affordable for clinical studies

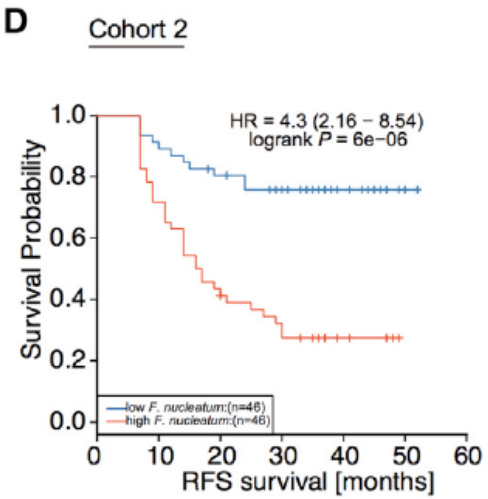
Rook G et al. Lancet, July 2017
Claesson MJ et al. Nat Rev Gastroenterol Hepatol, Aug 2017

Fusobacterium nucleatum (Fn) is associated with CRC recurrence and patient outcome



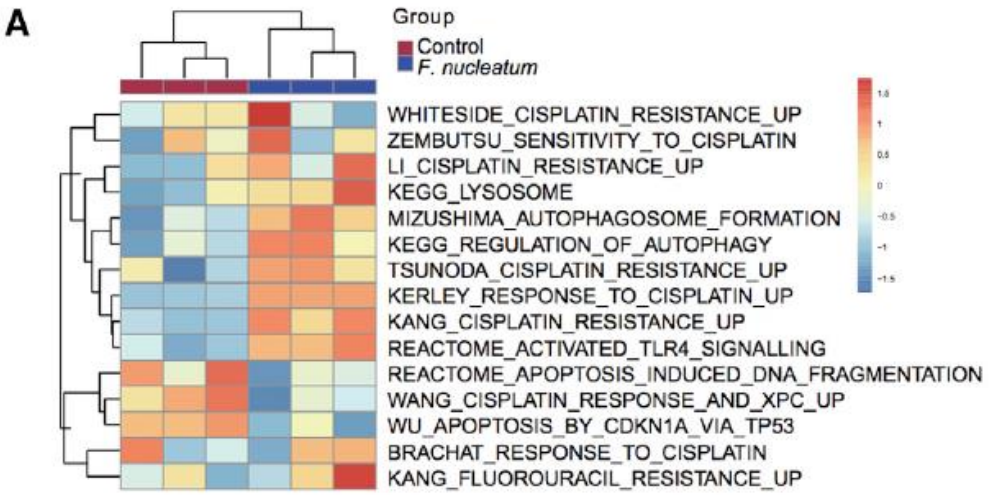






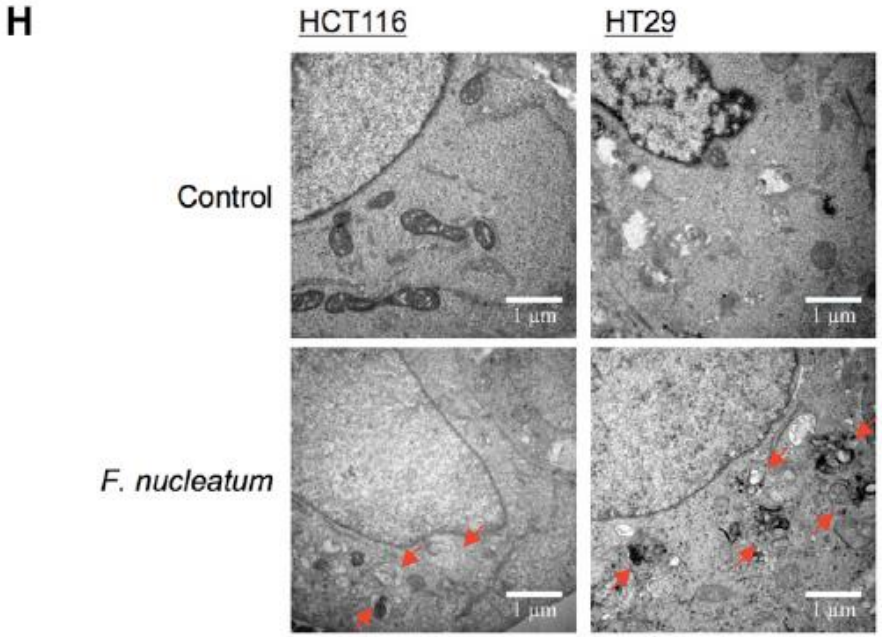
Yu T et al. Cell , July 2017

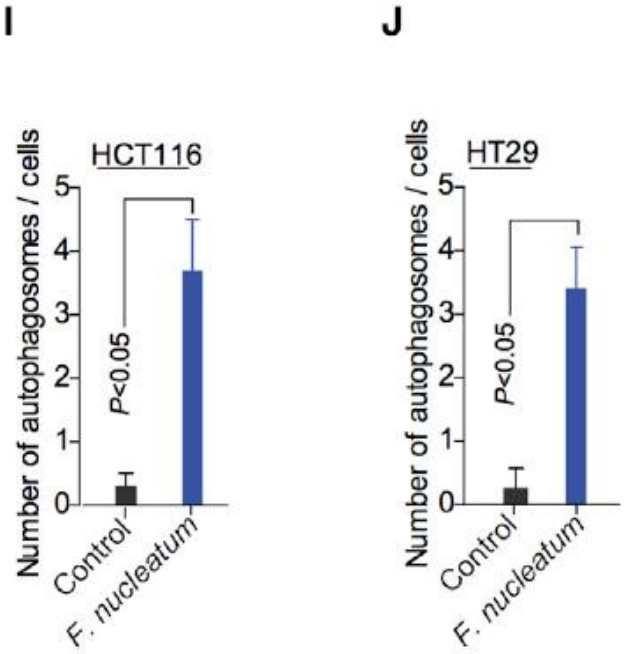
Fn promotes cancer autophagy activation



Co-culture with Fn:

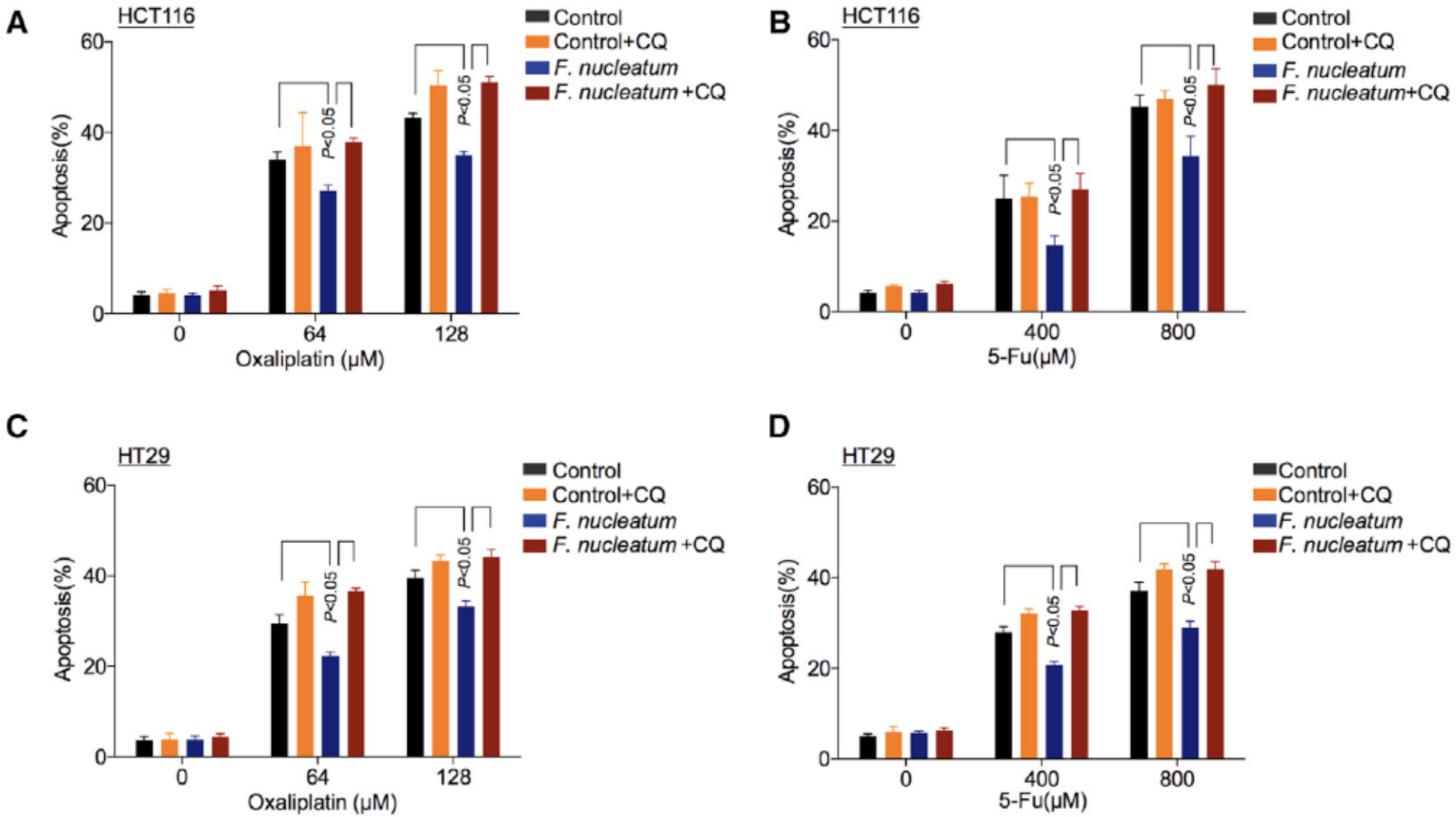
- 992 downregultaed gene
- 1,466 upregulated genes (*ULK1*, *ATG7*)





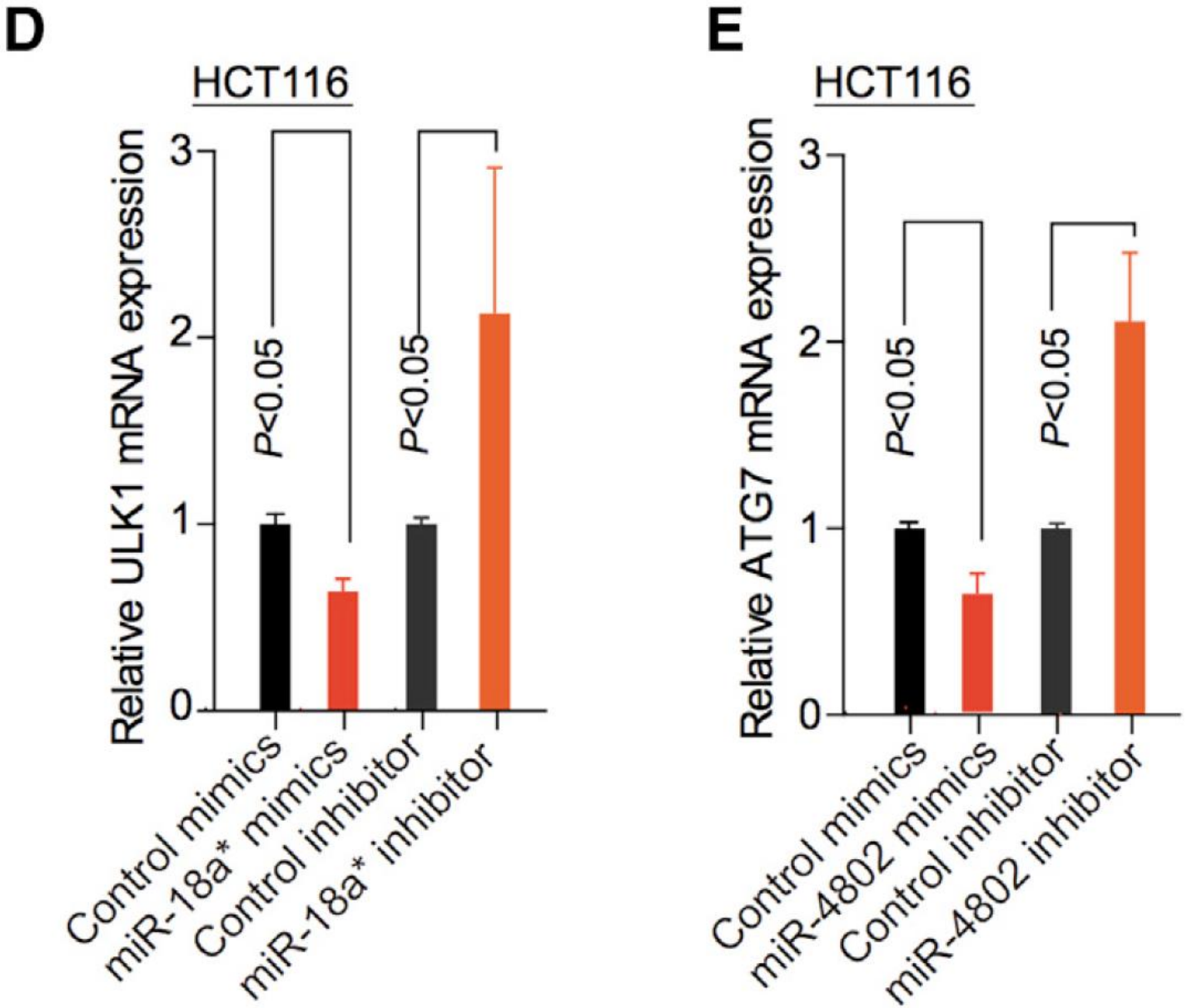
Yu T et al. Cell , July 2017

Fn induces cancer chemoresistance via autophagy pathway



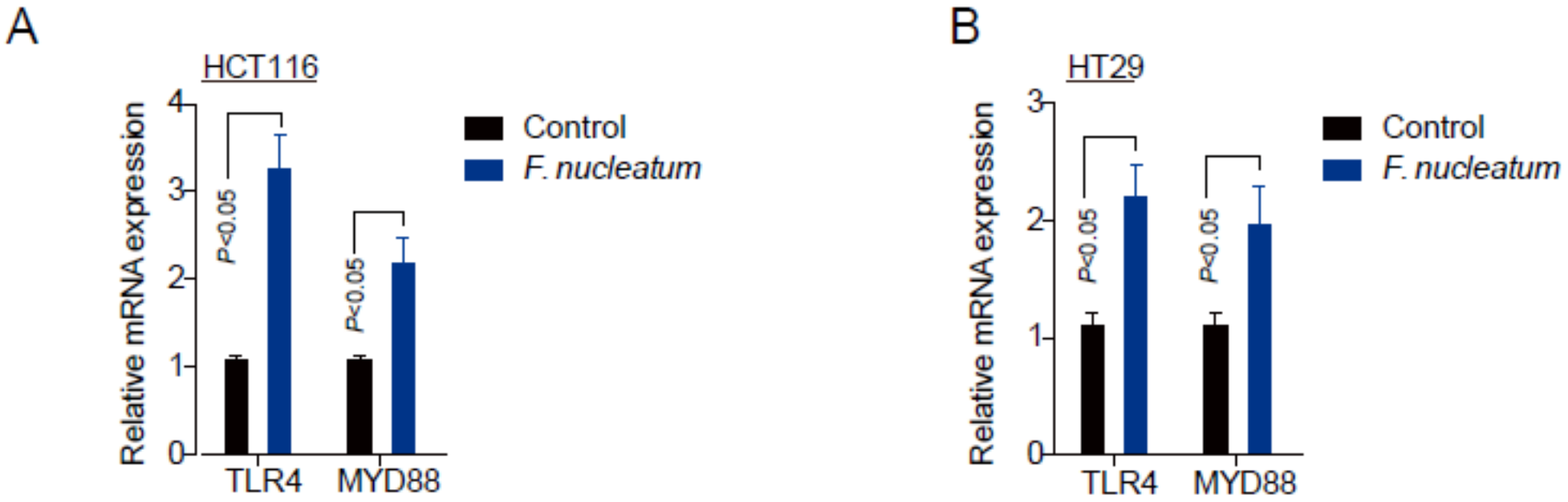
Yu T et al. Cell , July 2017

Fn activates cancer autophagy via selective loss of miR-18a* and miR-4802



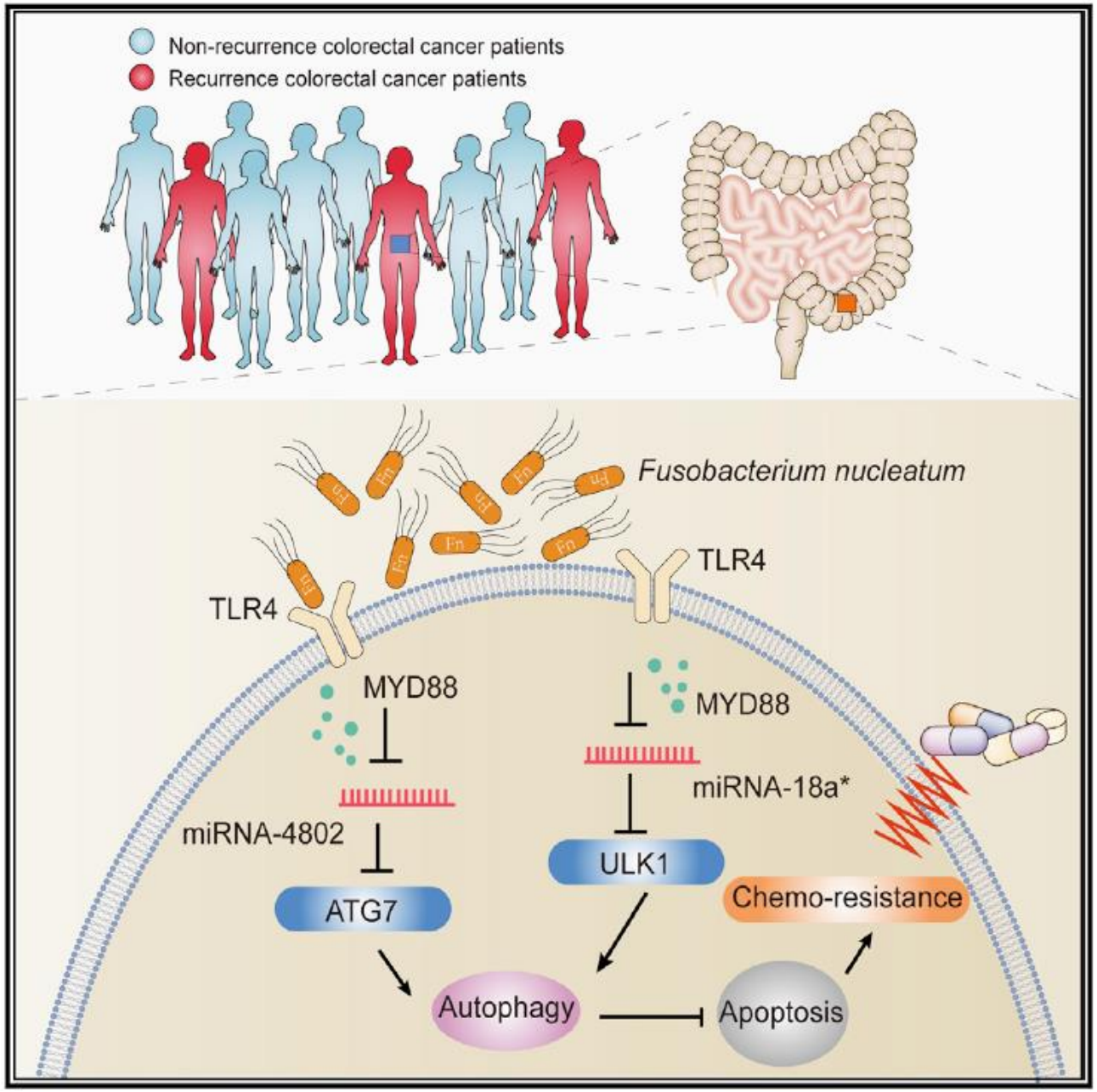
Yu T et al. Cell , July 2017

TLR4 and MYD88 Pathway Is Involved in Fn-Mediated Chemoresistance



Yu T et al. Cell , July 2017

Fn promotes Chemoresistence to CRC by Modulating Autophagy



Yu T et al. Cell , July 2017

Conclusions

- Genetics and Genomics are irrevocably changing the face of biomedical research and, more slowly, clinical medicine.

- Turning back now from the use of genomic technologies in health care is inconceivable.

- A wide approach to individual variability in environment, lifestyle and genes, will improve our capacity to diagnose, prevent and predict diseases.

- PM should be supervised only by a qualified physician and conducted only by scientifically qualified persons.

- Some major challenges:
  - . education
  - . to define "genetic test scenarios" and clinical guidelines
  - . to regulate DTC medical testing
  - . to develop precision approaches to interventions in individuals and populations