

Genomic medicine on cancer management - challenges for insurance industry

Dr David Lu, Deputy Regional Chief Medical Officer, Swiss Re

What is Genomic Medicine?

- An emerging medical discipline that involves **using genomic information** about an individual as part of their **clinical care** (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use.

The National Human Genome Research Institute

- Part of so-called precision, or personalised medicine.
- New techniques combined with the growing availability of genomic information and new predictive methodologies will challenge how we as insurers define and classify cancer; how we structure and price our policies; and how we sustainably provide our products and services to our customers.

Today's agenda

- The basics
- Genetic testing
- Liquid biopsy
- Gene therapy
- Challenges for insurance industry

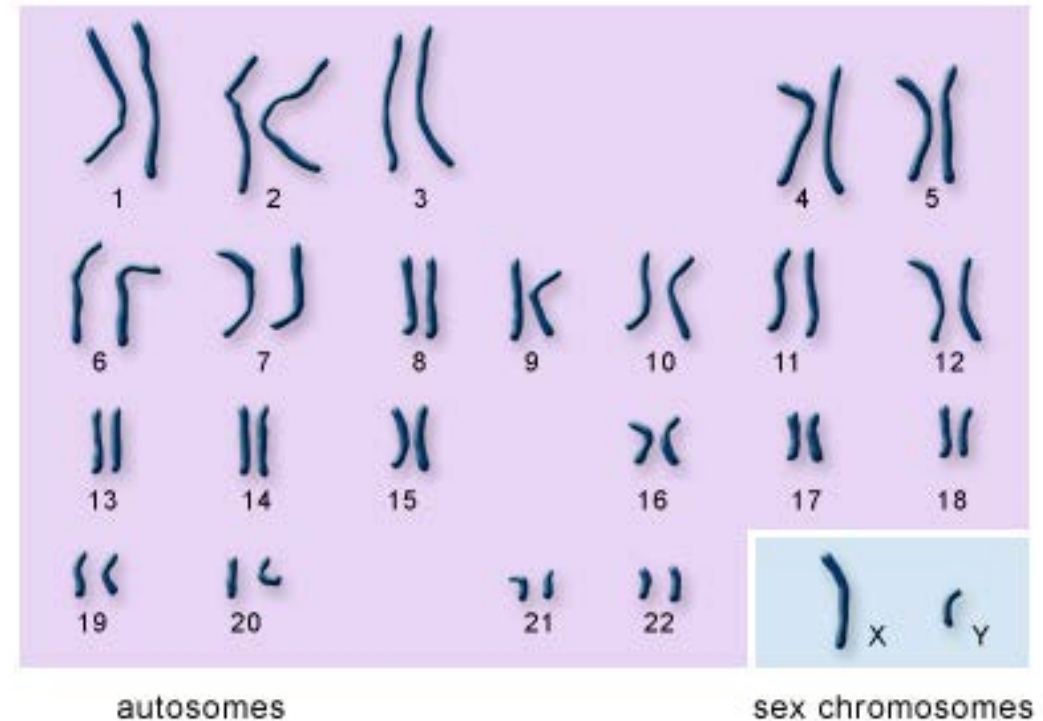
The basics

Chromosomes

Chromosomes are thread-like molecules that carry hereditary information for everything from height to eye color.



- Walter Sutton (left) and Theodor Boveri (right) independently developed the chromosome theory of inheritance in 1902.

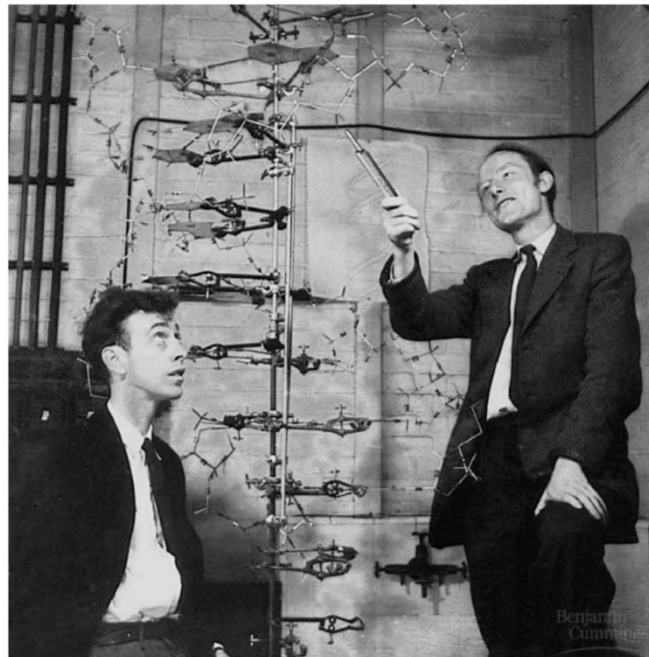


U.S. National Library of Medicine

Full set of human chromosomes – 23 pairs

DNA

DNA (deoxyribonucleic acid) is the genetic material of living organisms. It contains the instructions an organism needs to develop, live and reproduce.



1953, Watson & Crick proposed the DNA model

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

¹ Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).

² Longuet-Higgins, M. S., *Mon. Not. Roy. Astr. Soc., Geophys. Supp.*, **5**, 285 (1949).

³ Von Arx, W., S., Wedge Hole Papers in Phys. Oceanogr. Meteor., **11** (3) (1950).

⁴ Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1955).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β -D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furbert's² model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furbert's 'standard configuration', the sugar being roughly perpendicular to the attached base. There



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

is a residue on each chain every 3.4 Å. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphorus atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally^{3,4} that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

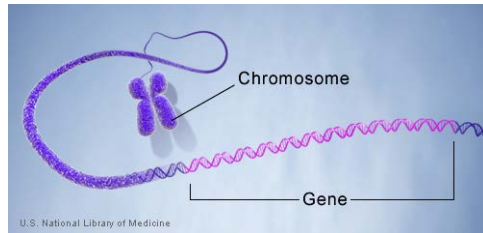
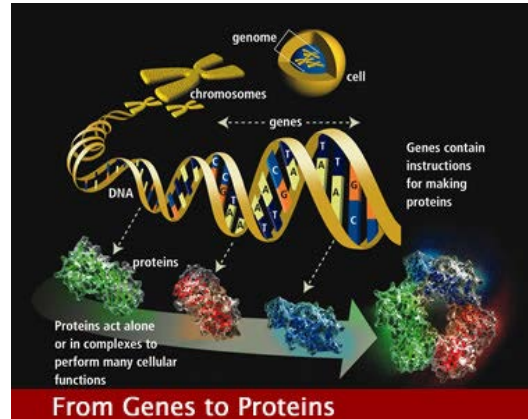
The previously published X-ray data^{5,6} on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

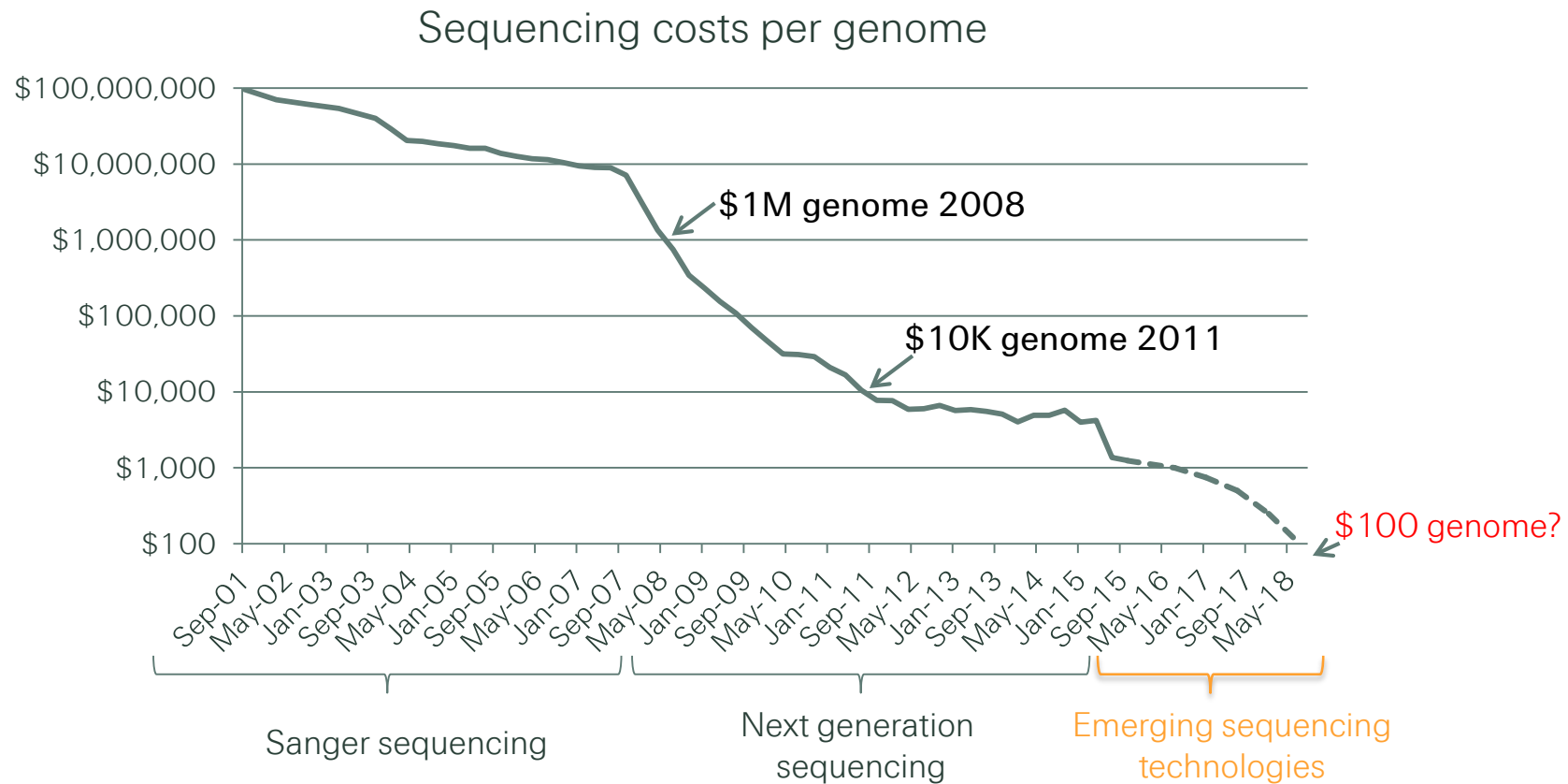
We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on inter-atomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

Gene and Genome



- **Genes** are sections of DNA which act as instructions to make proteins
- A **genome** is an organism's complete set of DNA including all genes. Genome contains all the information to build and maintain that organism.
- The **Human Genome Project (HGP)** was an international scientific research project with the goal of determining the sequence of nucleotide base pairs that make up human DNA, and of identifying and mapping all of the genes of the human genome from both a physical and a functional standpoint.
- HGP was formally launched in 1990 and was declared complete on April 14, 2003.

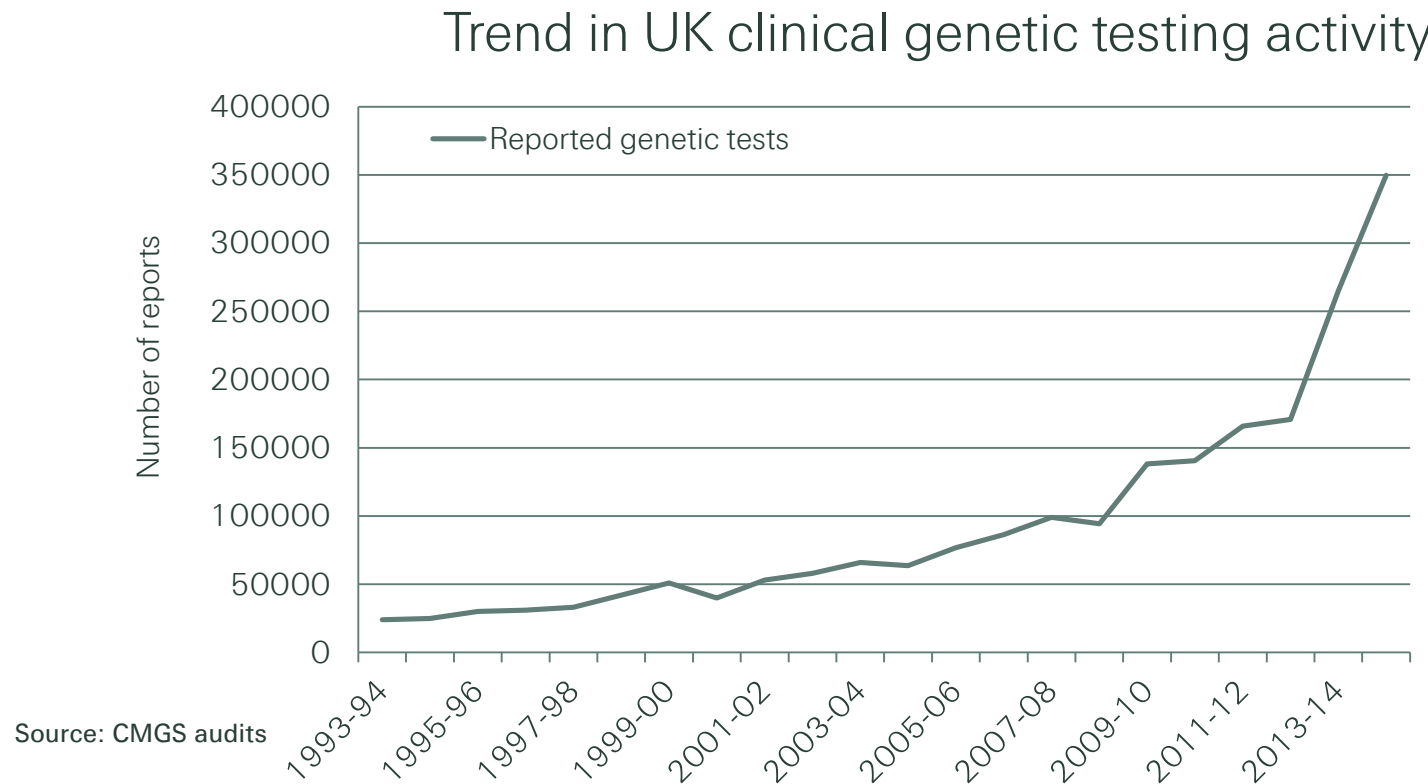
Full genome sequencing becomes affordable



Source: NIH National Human Genome Research Institute <http://www.genome.gov/sequencingcosts/>

Plummeting genome sequencing costs and advances in human genetics increases the availability for different types of genetic testing.

Genetic testing in the clinical practice grows at about 13% annually



Advances in the understanding of human genetics increases the availability and uptake of genetic testing in the clinical practice.

Genetic testing

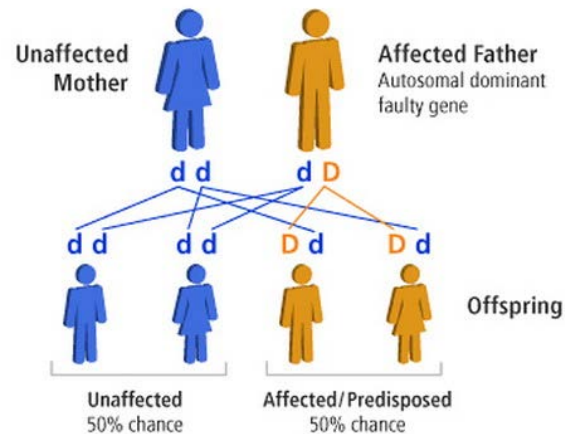
What is genetic testing?

Genetic testing looks for alterations in a person's genes or chromosomes to identify heritable or acquired mutations related to disease and health.

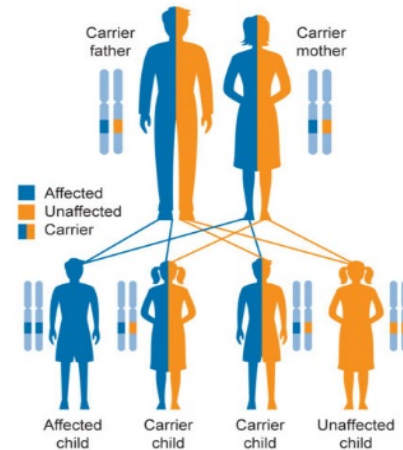
Mono-genetic disorders

- Mono-genetic disorders are caused by DNA changes in one particular gene, and often have predictable inheritance patterns.

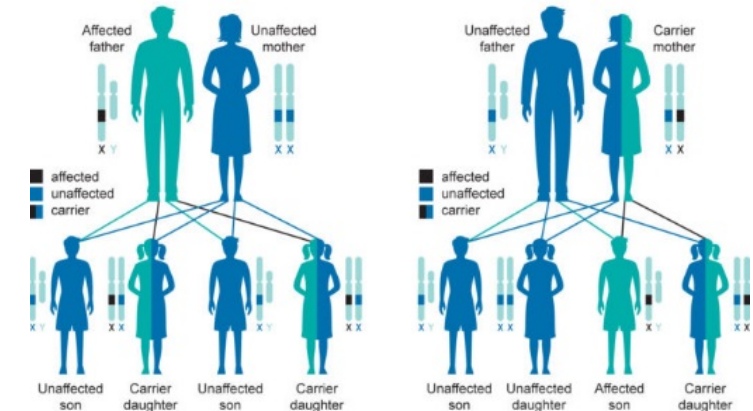
Autosomal dominant inheritance



Autosomal Recessive Inheritance



X-Linked Recessive Inheritance



Multifactorial and polygenic (complex) genetic disorders

Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause - they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors.

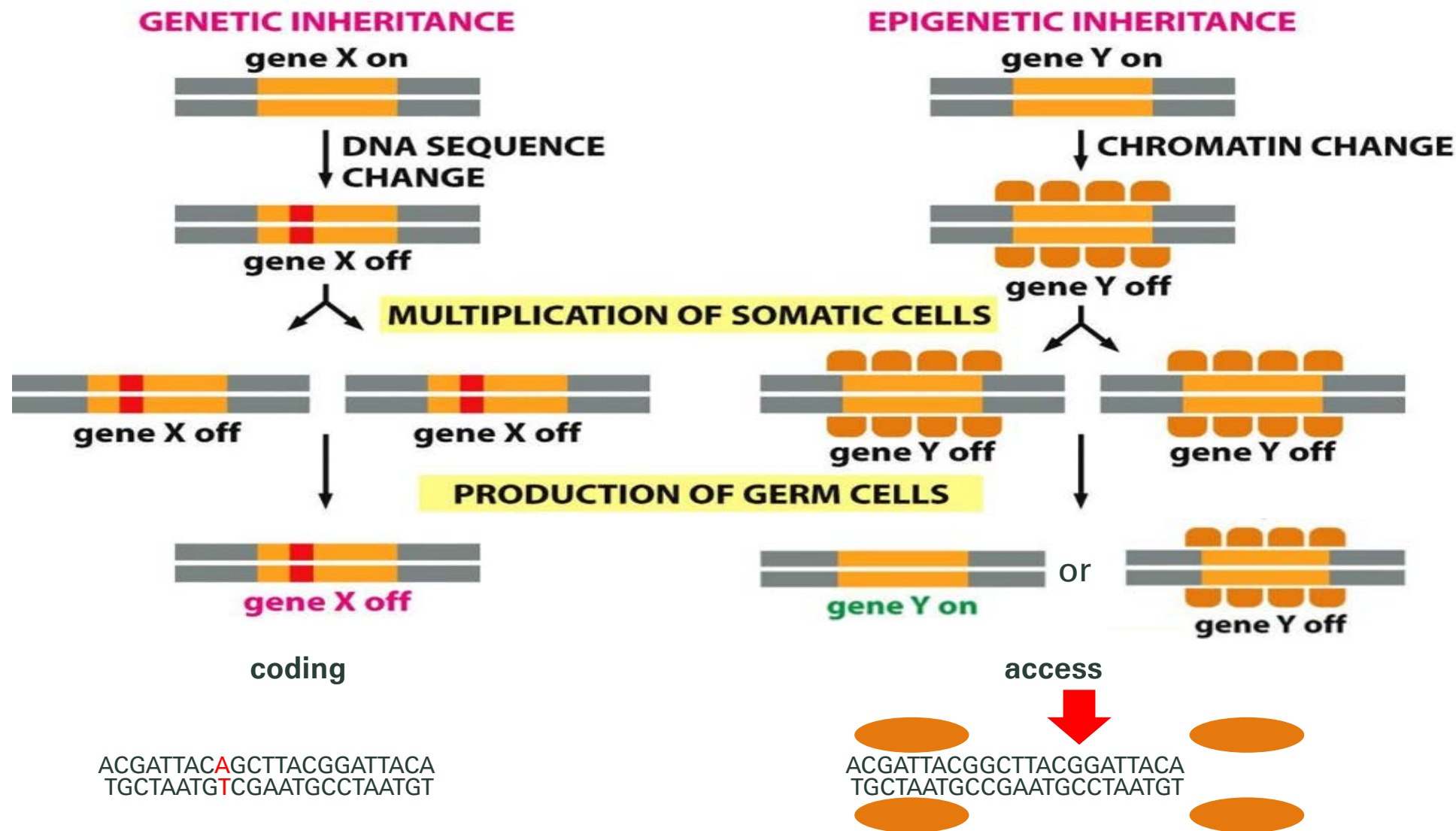
Use polygenic risk score (PRS or PGS) to predict future risk of polygenic genetic disorders has shown great potential.

Selected examples of available multi-gene NGS panels		# Genes
Cancer	Hereditary cancers (breast, colon, ovarian)	10-50
Cardiac diseases	Cardiomyopathies	50-70
	Arrhythmias (ex Long QT syndrome)	10-30
	Aortopathies (Marfan's syndrome)	10
Neurologic disorders	Parkinsons disease	30
	Alzheimers disease	30
	Epilepsy	53-120
	Muscular dystrophy	12-45

NGS=next generation sequencing

Rehm H, Nature Genetics 2013 14:295-300

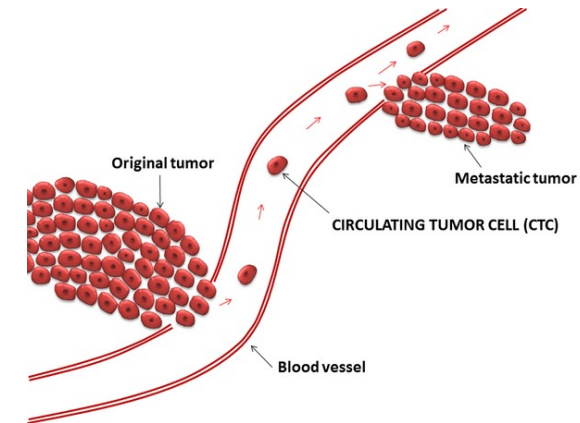
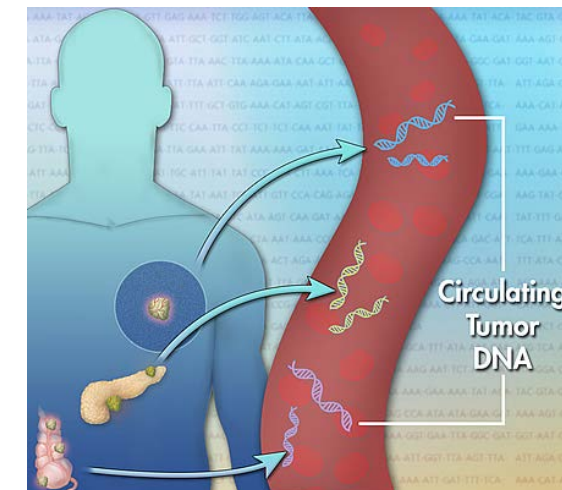
Genetic inheritance versus Epigenetic inheritance



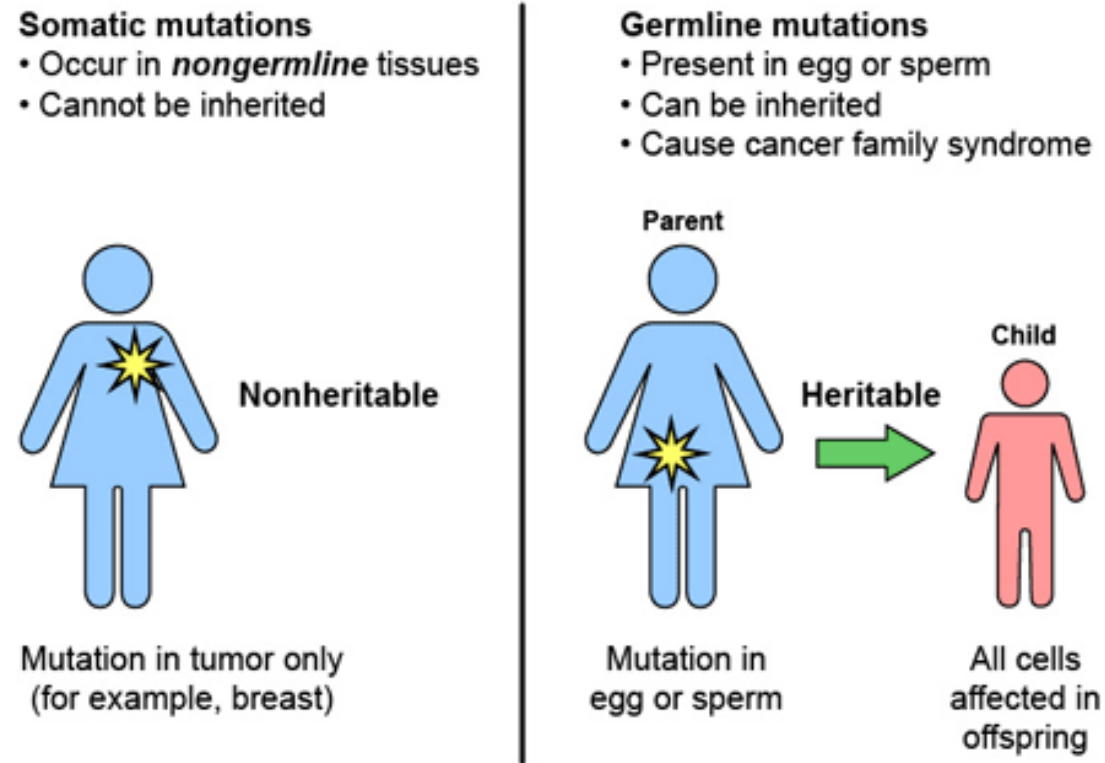
Liquid biopsy

What is liquid biopsy?

- To look for cancer cells from a tumor that are circulating **in the blood** or for pieces of DNA from tumor cells that are **in the blood**.
 - Liquid also include **CSF, urine and other body fluids**.
-
- Circulating tumour cells (CTCs)
 - Circulating tumour DNA (ctDNA)
 - exosomes – extracellular vesicles
 - tumour-educated blood platelets (TEPs)



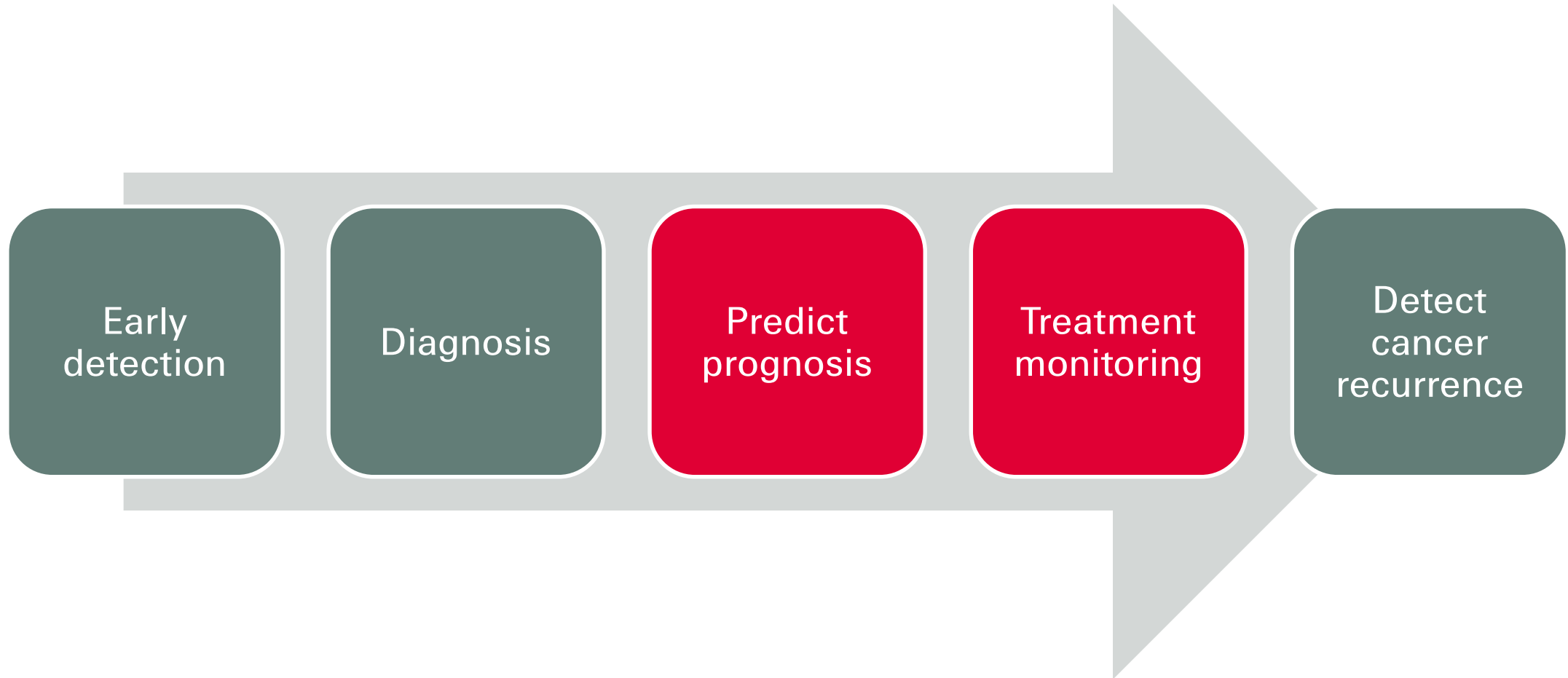
Liquid biopsy is looking for somatic mutation



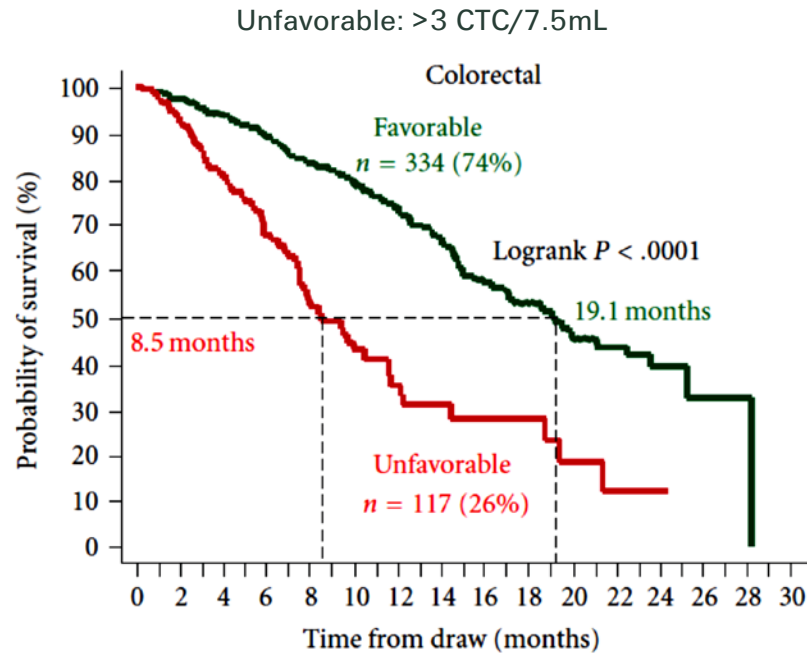
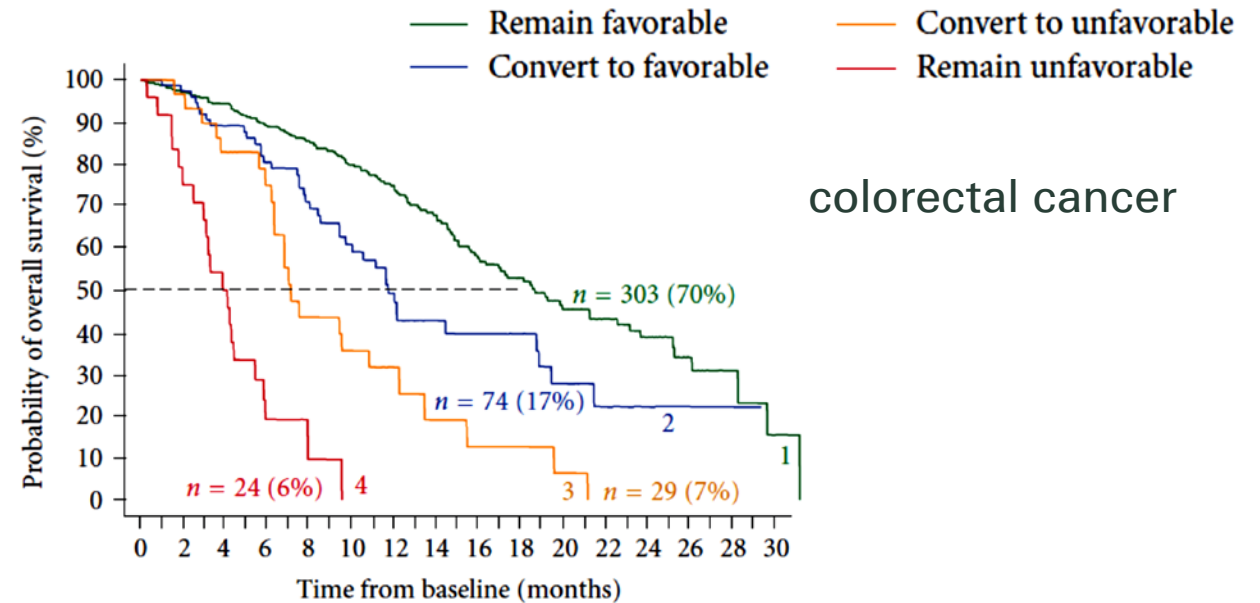
Adapted from the National Cancer Institute and the American Society of Clinical Oncology

- Somatic mutations develop after conception in any cell in the body, and are passed down only to descendants of that particular cell, not to future generations.
- Germline mutations are passed from generation to generation through the germ cells; they are present at conception and therefore are passed down into every cell in the body.

Liquid biopsy and cancer management



Predicting prognosis and monitoring treatments



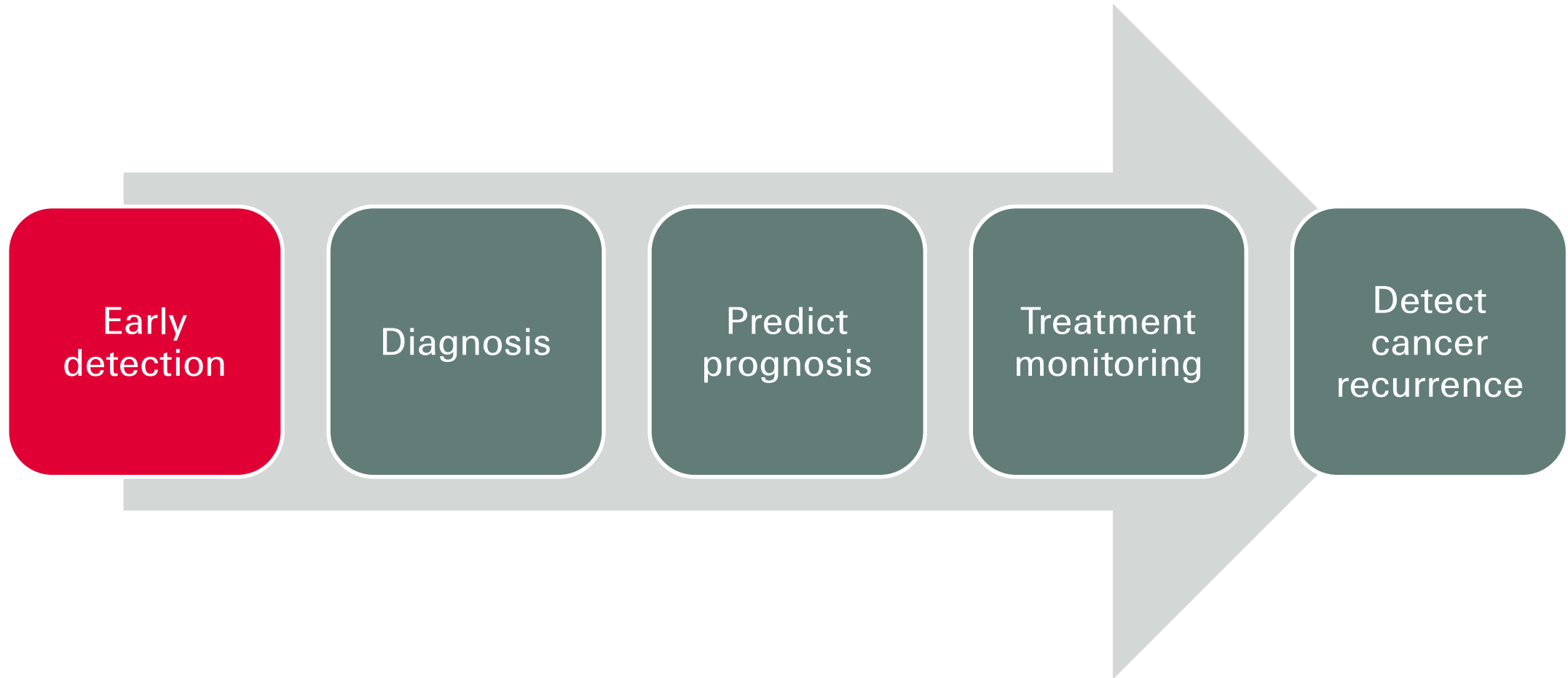
colorectal cancer

- The number of CTCs links to survival.
- Persistent CTCs after treatment correlated with unfavorable prognoses.

CellSearch system was approved by the FDA in 2004 to predict outcomes for metastatic breast cancer patients, and to aid in monitoring colorectal (2007) and prostate cancer (2008) patients.

MC Miller, et al. Journal of Oncology 2010: 1–8

Liquid biopsy and cancer management



CTCs were detected 1-4 years earlier than CT for lung cancer

Table 2. Clinical and pathological characteristics of CTC-positive COPD patients.

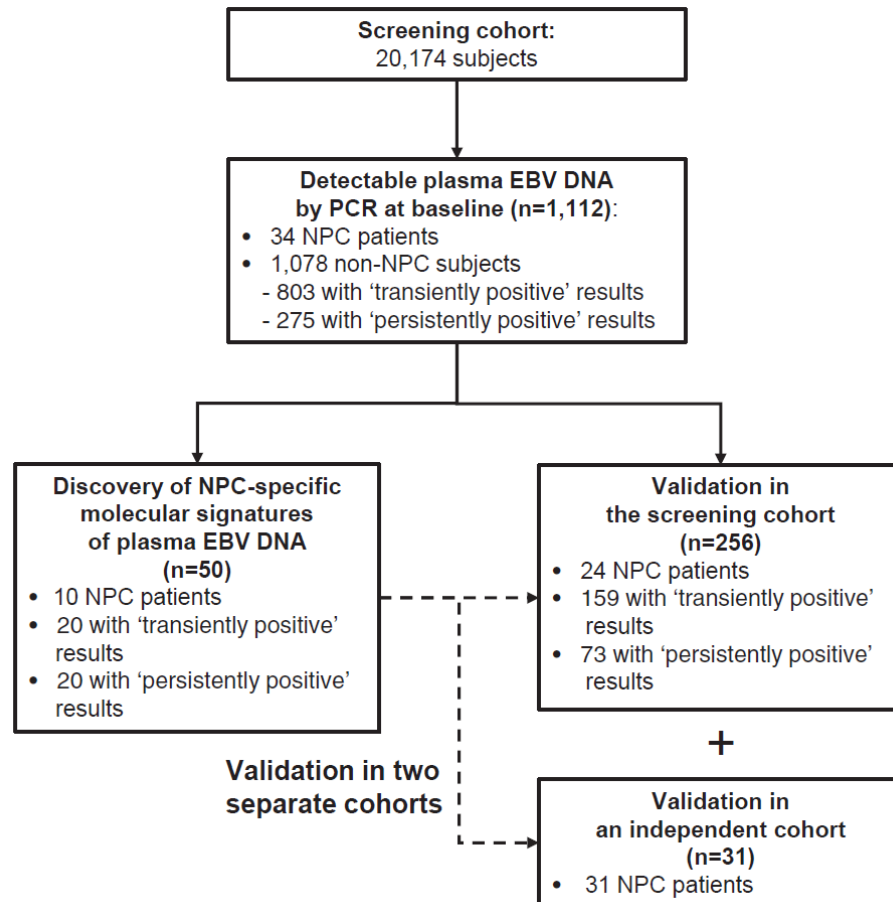
Patients	Sex	Age (years)	Smoking status (PY)	Year of COPD diagnosis	GOLD score	Year of CTC Detection (Study entry)	CTCs/CTM		Year of Lung cancer diagnosis	Lung Cancer size (cm)	Histology	Stage	Mutation tumor status	One-year follow-up after surgery
							CTCs	CTM						
P1	M	54	60	1998	3	2009	43	1	2012	1.9	Invasive papillary adenocarcinoma	IA	KRAS p.Gly12Cys	No recurrence
P2	F	48	45	1995	2	2009	67	3	2010	1.5	Invasive papillary adenocarcinoma	IA	KRAS p.Gly12Val	No recurrence
P3	M	47	35	1999	2	2008	32	1	2012	1.4	Invasive acinar adenocarcinoma	IA	KRAS p.Gly12Cys	No recurrence
P4	M	52	45	1994	3	2009	19	1	2013	2	Squamous cell carcinoma	IA	STK11 (missense mutation)	No recurrence
P5	M	63	55	2001	3	2009	28	1	2013	1.5	Invasive acinar adenocarcinoma	IA	No mutation	No recurrence

* CTM: circulating tumor microemboli, a cluster of cancer cells

Ilie M, Hofman V, Long-Mira E, Selva E, Vignaud J-M, et al. (2014) "Sentinel" Circulating Tumor Cells Allow Early Diagnosis of Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease. PLoS ONE 9(10): e111597. doi:10.1371/journal.pone.0111597

Sequencing-based counting and size profiling of plasma Epstein–Barr virus DNA enhance population screening of nasopharyngeal carcinoma

W. K. Jacky Lam^{a,b,c,d,1}, Peiyong Jiang^{a,b,c,1}, K. C. Allen Chan^{a,b,c,1}, Suk H. Cheng^{a,b}, Haiqiang Zhang^{a,b}, Wenlei Peng^{a,b}, O. Y. Olivia Tse^{a,b}, Yu K. Tong^{a,b}, Wanxia Gai^{a,b}, Benny C. Y. Zee^e, Brigitte B. Y. Ma^{c,f}, Edwin P. Hui^{c,f}, Anthony T. C. Chan^{c,f}, John K. S. Woo^d, Rossa W. K. Chiu^{a,b,c}, and Y. M. Dennis Lo^{a,b,c,2}



Extrapolated performance of the new protocol

Sensitivity : 97.1% (CI: 85.1 – 99.9%)
 Specificity : 99.3% (CI: 99.2 – 99.4%)
 False positive rate : 140 / (20174-34-1)
 = 0.70% (CI: 0.59 – 0.82%)

Positive predictive value: 19.5% (CI: 13.9 – 26.2%)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5984543/pdf/pnas.201804184.pdf>

Grail raises more funds to advance a blood-based cancer test

Flush with another \$300 million, Grail plans to enroll 135,000 people in studies this year to detect circulating tumor-derived DNA

by *Ryan Cross*

MAY 22, 2018 | APPEARED IN **VOLUME 96, ISSUE 22**

In the meantime, **Grail will launch its first commercial blood test, for nasopharyngeal cancer, in Hong Kong**, where the disease is prevalent. Grail obtained the blood test when it merged with the Hong Kong-based company Cirina in May 2017.

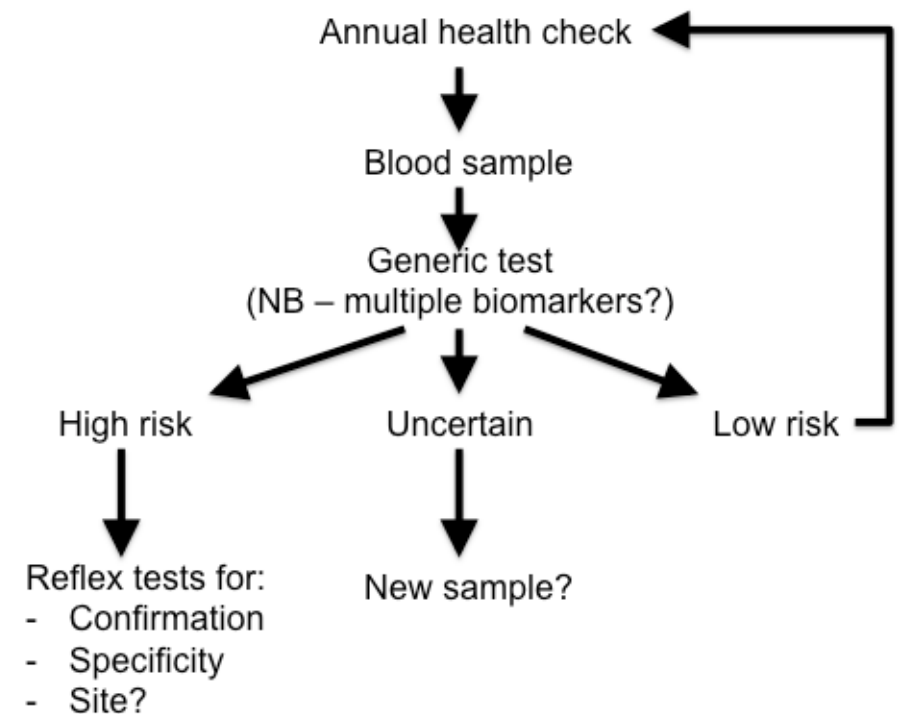
<https://cen.acs.org/business/startUps/Grail-raises-funds-advance-blood/96/i22>

UK nation wide project

Research Paper

Building the Evidence Base of Blood-Based Biomarkers for Early Detection of Cancer: A Rapid Systematic Mapping Review

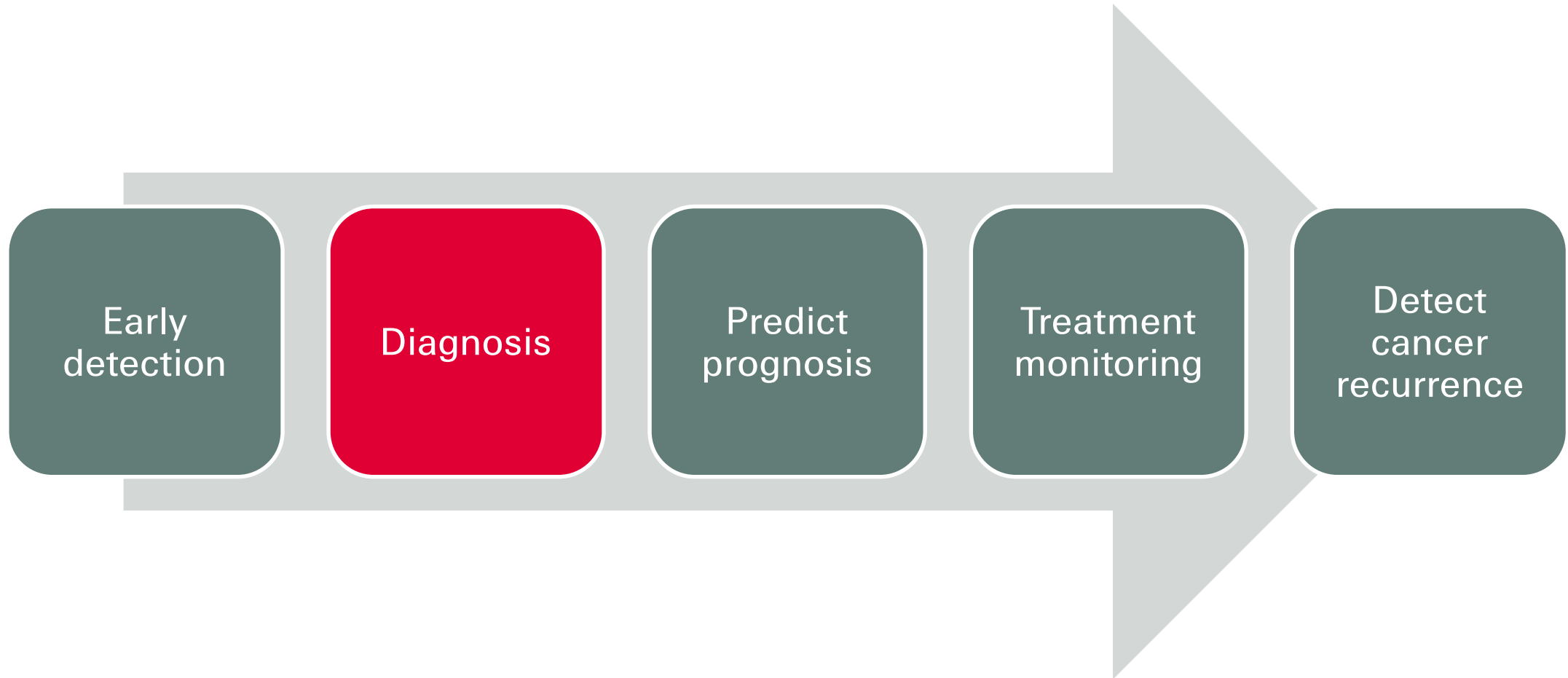
- This review resulted in a final list of 788 cancer biomarkers.
- **Early Cancer Detection Consortium** is funded by **Cancer Research UK**
- The ultimate goal is to produce a strategy for generic cancer screening that can go into clinical practice.



<http://www2.warwick.ac.uk/fac/med/about/centres/uk-ecdc/>

EBioMedicine. 2016 Aug;10:164-73. doi: 10.1016/j.ebiom.2016.07.004. Epub 2016 Jul 6.

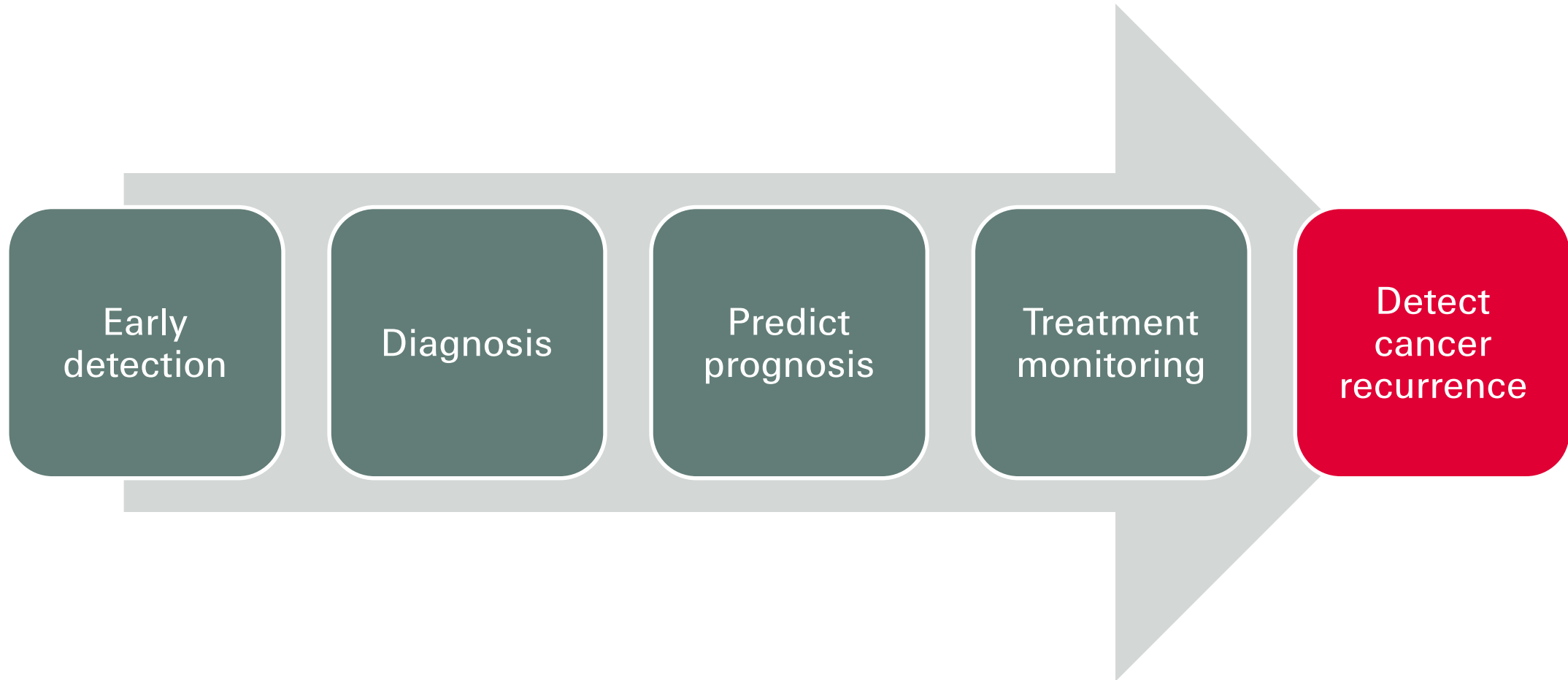
Liquid biopsy and cancer management



Cancer definitions for critical illness

- Tissue biopsies (histopathology) presently remain the gold standard.
- Cancer definitions vary by market. Although most definitions explicitly require histopathological proof, some products only require pathology, rely on ICD coding or accept clinical diagnosis and would be less protected against a new wave of liquid biopsy diagnosis.
- Using explicit liquid biopsy exclusions in definitions could act as a safeguard.

Liquid biopsy and cancer management



Detecting recurrence earlier than imaging

- In patients with non-metastatic cancers, ctDNA-based liquid biopsies could be optimized to **capture** and monitor genomic markers of **Minimal Residual Disease** following curative resection, possibly **preceding** the development of **clinical or radiologic recurrence**.
- **Early detection** of small micrometastatic lesions that are **currently undetectable by clinical imaging procedures** (CT or MRI scans) would largely increase the chances to prevent full-blown, incurable metastatic disease.
- CTC- and ctDNA-based screening of patients with higher risk of relapse may create opportunities for **therapeutic interventions before the development of clinical metastasis**.

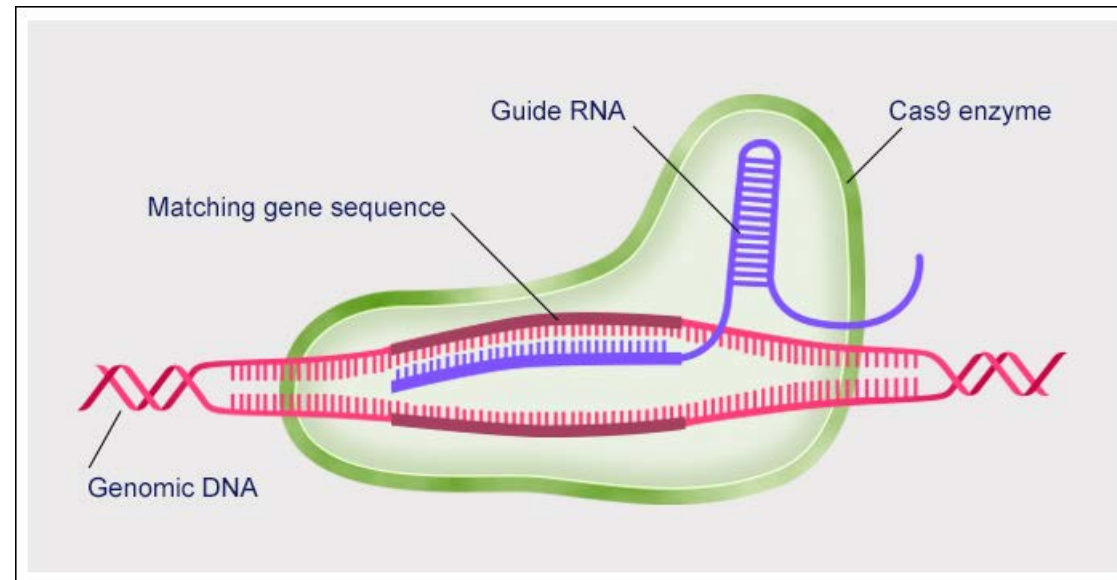
Cancer Cell 31, February 13, 2017

Gene therapy

What is gene therapy?

- The FDA defines gene therapy as a medicine that “introduces genetic material into a person’s DNA to replace faulty or missing genetic material” to treat a disease or medical condition.

Gene editing with CRISPR/Cas9



The “first gene therapy” approved by FDA

FDA Approves Groundbreaking Gene Therapy for Cancer

The treatment will be sold by Novartis for \$475,000.

by Emily Mullin August 30, 2017

Novartis' Kymriah, the first approved CAR-T therapy worldwide, has performed far below sales expectations in the last quarter. The news highlights the challenges CAR-T therapies still face before becoming a commercially viable treatment option.

In the first quarter of 2018, the treatment brought in \$12M, roughly **four times below the sales** needed to meet analyst **expectations**.

The question reflects one of the biggest challenges for cell and gene therapies: **pricing**.

<https://labiotech.eu/kymriah-car-t-therapy-novartis-sales/>

- CAR-T therapy, marketed as Kymriah
- A patient's T cells are extracted and cryogenically frozen so that they can be transported to Novartis's manufacturing center.
- There, the cells are genetically altered to have a new gene that codes for a protein—called a chimeric antigen receptor, or CAR. This protein directs the T cells to target and kill leukemia cells with a specific antigen on their surface.
- The genetically modified cells are then infused back into the patient.
- It takes an average of 22 days to create the therapy, from the time a patient's cells are removed to when they are infused back into the patient.

Challenges for insurance industry

Interest in testing, disclosure and actions to be taken

Studies in affinity groups who have an interest in a specific genetic condition ([registrants at Alzheimer's Prevention Registry](#))

n=4036 mean age 58, 81% women 66.2% college grads

78% perceived themselves to be at higher risk for AD. This could bias the group to potentially be more open to testing

Testing that reveals future risk of AD

Important to be tested	70.4%
If required for research would you be tested?	94.9%
Do you want results if collected for research?	88.7%
If insurance paid for test	80.8%
If it cost you >\$100	58.7%

Who you would disclose result to

Spouse	92.3%
Siblings	84.6%
Children	81.7%
Physician	79.4%
Lawyer	60.5%

If you were at high risk for AD would you

Begin a healthier lifestyle	90.5%
Get LTC insurance	76.3%
Spend all of your money for pleasure	18.4%
Seriously consider suicide	11.6%

Studies on genetic testing and its impact on insurance purchasing behaviour

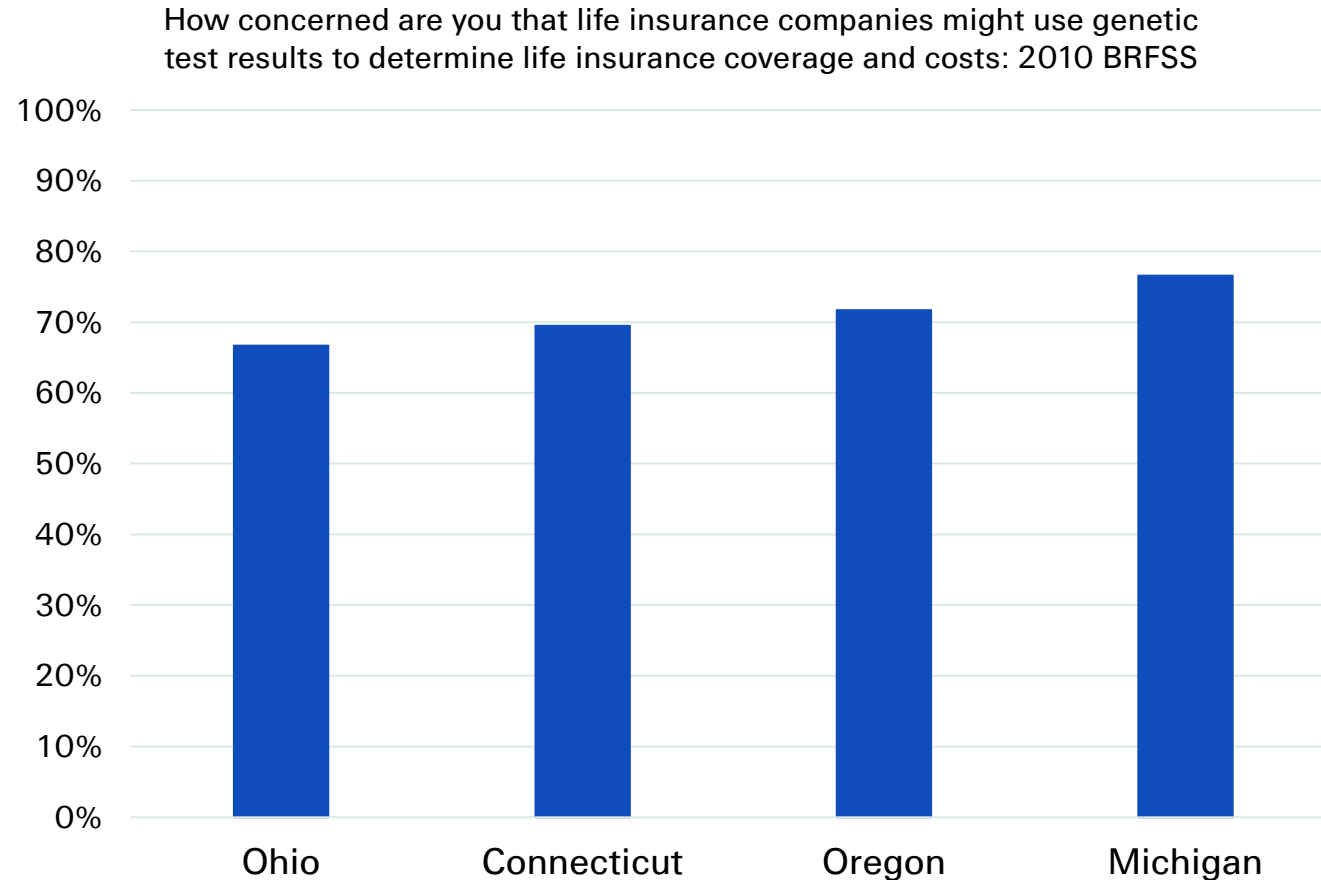
Genetic disease (Gene)	Insurance product	Odds ratio of over-insuring after positive test	Study
Breast cancer (BRCA1/2)	Life insurance	5.1x more likely to increase coverage	Armstrong et al.; 2003 (USA)
Alzheimer's disease (APOE4)	Long-term care insurance	5.7x more likely to change coverage	Taylor et al.; 2005 (USA)
Alzheimer's disease (APOE4)	Long-term care insurance	2.3x more likely to increase coverage	Zick et al.; 2010 (USA)
Huntington's disease (HD)	Long-term care insurance	5x more likely to purchase insurance	Oster et al.; 2010 (USA & Canada)
Colorectal cancer (HNPCC)	Life insurance	1.3x more likely to purchase insurance	Aktan-Collan et al.; 2001 (Finland)

Understanding of consumers acceptance of and concerns about genetic testing is key to investigate the potential impact on insurance purchasing behaviour and level of adverse selection against insurers.

Concerns on insurance company using genetic test results for underwriting

Four states added questions on genetic testing to the Behavioral Risk Factor Surveillance System health survey.

The results indicate the majority are concerned about the use of genetic test results by life insurance companies.



Parkman A, et al., J Genet Counsel 2015, 24:512-521

Insurers are faced with various levels of restriction on use of genetic data in different countries

**Protection
of
genetic
data**

Belgium
France
Austria
Portugal
Ireland

Germany
Switzerland
Netherlands
UK
Sweden

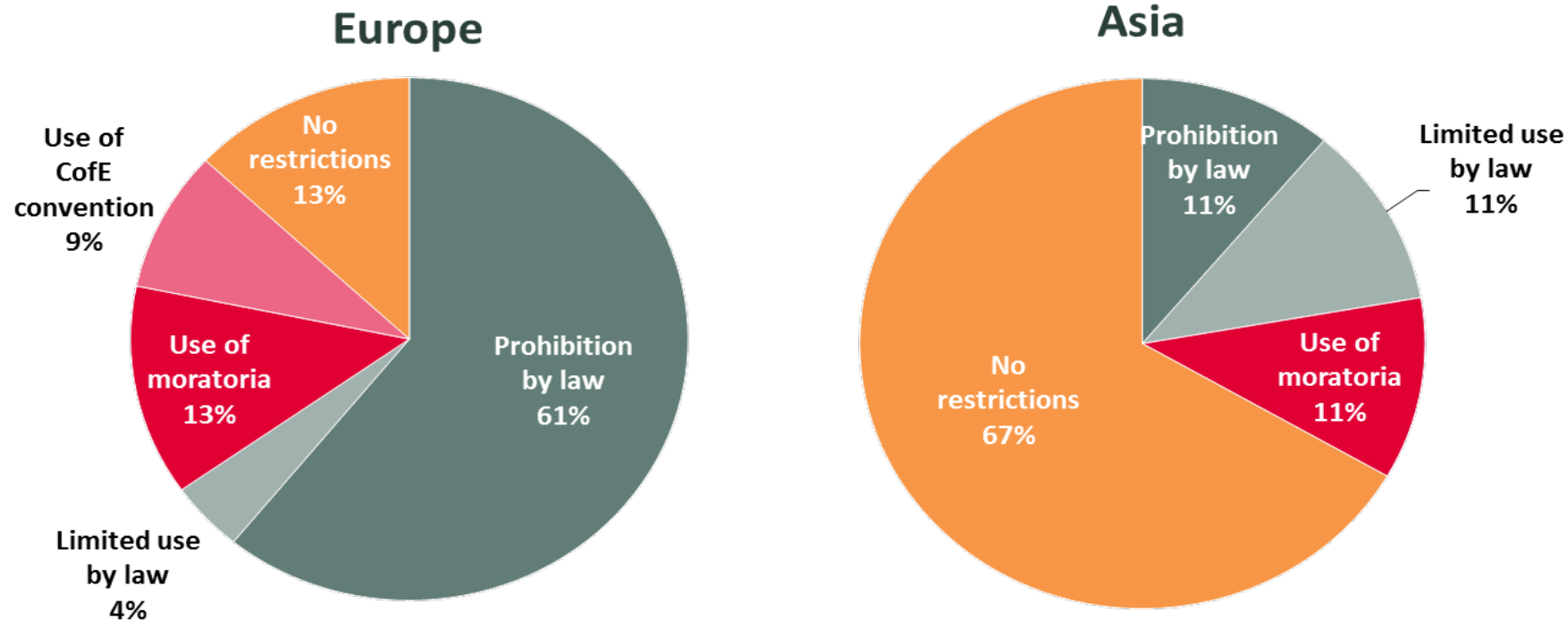
USA
Canada
Australia
South Africa
Italy

**Genetic
data
considered
medical
data**

Legislative regulations range from voluntary moratoria, legislation to strict outright bans and approaches continue to evolve.

Can insurers make use of genetic test results if presented at application stage?

Swiss Re global survey results 2013*



Numerous restrictions are in place in Europe while fewer restrictions exist in Asia; mainly self-regulated

* 23 EU countries and 7 other European countries included, alongside 10 Asia and a single African country

How real of a concern is adverse-selection from genetic testing?

Canadian Institute of Actuaries (CIA)

- as a result of the prohibition in access to predictive genetic testing information in Canada, the total death claim costs for life insurance would increase by 12% and critical illness claim costs are likely to increase by about 26% overall (+16% for males and +41% for females).

Impacts on insurance

Impacts

Anti-selection

Over-diagnosis, detect clinical indolent cancer, increase cancer incidence rate (diagnose rate)

Over-investigations, increase in medical expenses

Cancer shift to early stage, even pre-clinical stage

Better survival

Expensive gene therapy

Direct-to-Consumer test: mis-interpretation, not considered as medical evidence

Recurrence / cancer existence definition may change

Legal risk / reputation risk

Thanks



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