Precision Prediction

Qianyi Xiao, Ph.D.

Outline

- Heredity and Gene
- Precision medicine
- Precision prediction and prevention
- The ethic of genetic testing

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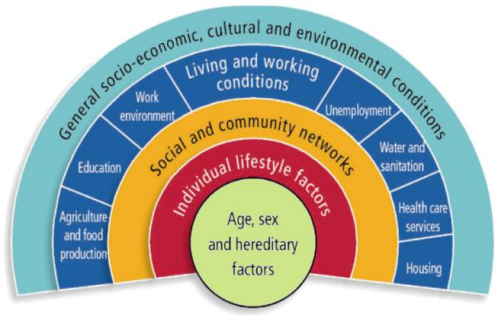
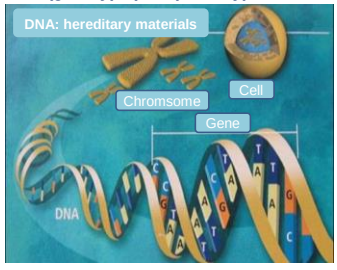
Health ecological model



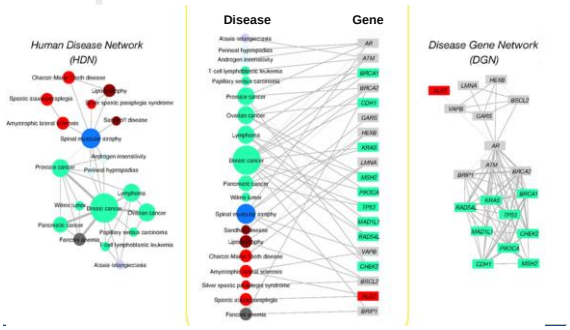
Gene

- Gene is a region of DNA and is the molecular unit of heredity
- Genetic traits (genotype)——phenotypic traits （phenotype）



Gene has become the focus of media

Disease Gene Network



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- **Precision medicine**
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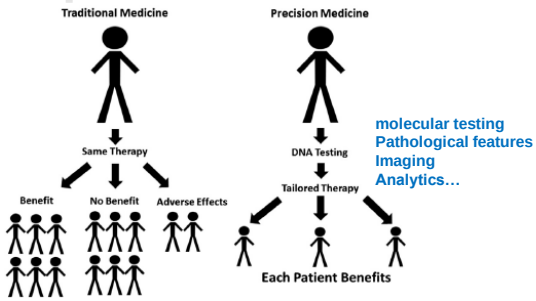
Precision Medicine



Precision Medicine

- **Precision medicine**

Precision medicine (PM) is a medical model that proposes the personalized treatment. In this model, molecular testing is often employed to select appropriate and optimal therapies based on the context of a patient's genetic content, or other molecular or cellular featrues.

Precision Medicine

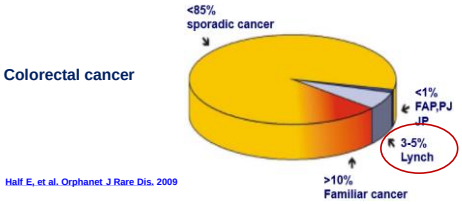
- **Molecular diagnosis**
- **Disease stratification**
- **Precision Therapy**
- **Complicated disease treatment**

Precision Medicine

- **Molecular diagnosis**
  - Hereditary cancer syndromes, rare hereditary disease.
  - Approximately 5–10% of all cancers are inherited.
  - Mainly caused by inherited gene mutations, which have highly penetrance.

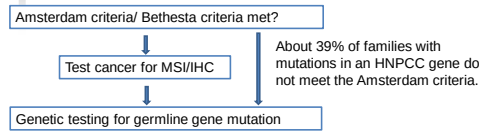
Clinical diagnosis for hereditary diseases

- ***Lynch Syndrome*** , also known as HNPCC (Hereditary Non-Polyposis Colorectal Cancer), is the most common hereditary colorectal cancer with a penetrance of 85–90%.
- Lynch Syndrome is caused by a germline mutation in any one of five DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS1, and PMS2)



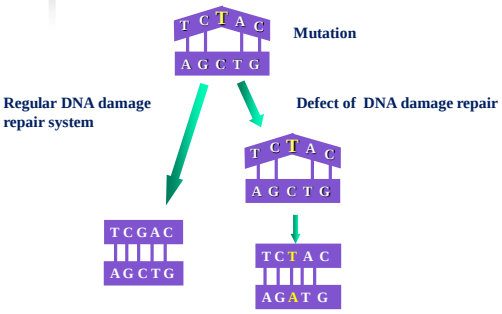
Half E, et al. Orphanet J Rare Dis. 2009

Lynch Syndrome diagnosis



- **Patients met Amsterdam criterial or Bethesda criteria test tumor tissue for MSI/IHC**
- **MSI (microsatellite instability)and IHC testing can define which patients should further pursue germline DNA mutational analysis.**
- **Once a specific mutation is identified, the diagnosis of Lynch syndrome is confirmed.**

Mechanism of MMR carcinogenesis ——DNA damage repair



Hereditary cancer syndrome

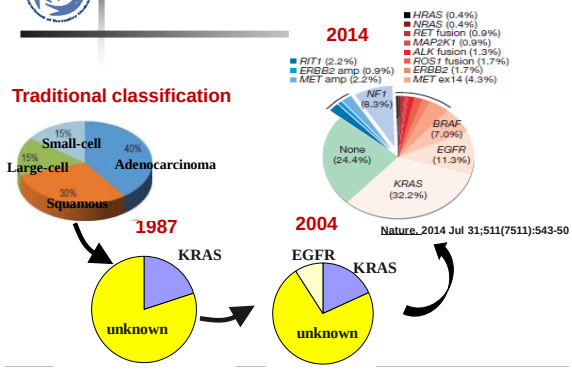
Disease	Gene	Related cancer
Hereditary breast-ovarian cancer syndrome (HBOC)	BRCA1，BRCA2	Breast cancer Ovarian cancer
Lynch Syndrome，/ Hereditary Non-Polyposis Colorectal Cancer（HNPCC）	MLH1,MSH2,MSH6, PMS2，ECAP	Colorectal cancer, endometrial cancer, gastric cancer, ovarian cancer,
Familial adenomatous polyposis（FAP）	APC	Colorectal cancer, Colorectal adenomatous polyposis
Hereditary diffuse gastric cancer (HDGC)	CDH1	Gastric cancer

Precision Medicine

- Molecular diagnosis
- **Disease stratification**

Molecular typing

Molecular typing of lung cancer



Nature. 2014 Jul 31;511(7511):543-50

Precision Medicine

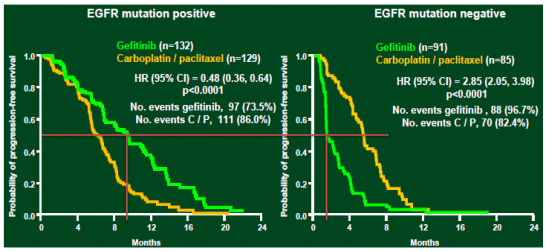
- Molecular diagnosis
- Disease stratification
- **Precision Therapy**

The design of drugs that target specific pathogenic mutations may improve the success of precision medicine

Precision Therapy

Lung adenocarcinoma

EGFR mutation in tumor is a strong predictor of a better outcome with gefitinib.



Mok, NEJM 2009

Precision Medicine

- Molecular diagnosis
- Disease stratification
- Precision Therapy
- **Complicated disease treatment**

Complicated disease treatment


The New York Times

Genetic Gamble

In Treatment for Leukemia, Glimpses of the Future

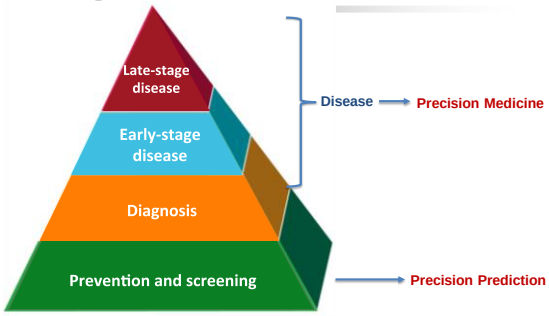
Gene may be the primary factor in the treatment of cancer, not just on the basis of cancer tissue or organ itself.

In Washington University， Dr. Lukas Wartman had acute lymphoblastic leukemia (ALL). He was deteriorating fast. No known treatment could save him.

Dr. Timothy Ley performed the DNA sequencing the RNA sequencing of both his cancer cells and healthy cells for comparison. And they found that a normal gene (FLT3) was wildly active in the leukemia cells.

Even better, there was a new drug, that approved for treating advanced kidney cancer, could shut down the malfunctioning gene.

How precision prediction might work ?



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- **Precision prediction and prevention**
- The ethic of genetic testing

Three Stage of Prevention

- **In predisease stage** — **Primary prevention**: Method to modify the risk factors in a favorable direction.
- **In latent disease stage** — **Scondary prevention**: Methods to detect and address an existing disease prior to the appearance of symptom.
- **In symptomatic disease stage** — **Tertiary prevention**: Methods to reduce the harm of symptomatic disease through rehabilitation and treatment.

How precision prediction might work ?

Genetic marker can be used in precision prediction

(1) Primary prevention (modifing the risk factors)

(2) Secondary prevention (screening program)

(3) Tertiary prevention (disability limitation)

Precision Prediction

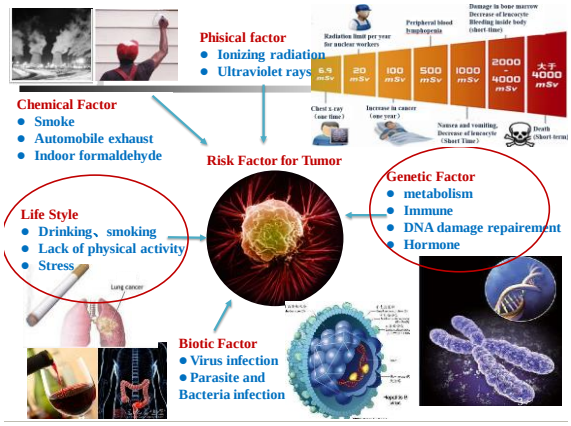
(1) Primary prevention

- helping to predict a person's susceptibility to adverse lifestyle exposures.

Interaction between Genetic and Environmental Risk Factors

Complicated disease are caused by the interaction between genetic predisposition and modifiable environmental factors

- Risk factor
  - Environmental factors (internal cause)
    - Chemical Factor
    - Physical factor
    - Life Style
    - Biotic Factor
  - Genetic factors (external cause)



Interaction between Genetic and Environmental Risk Factors

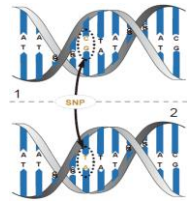
1. Disease that were determined by genetic factors
   - Hereditary syndrome
2. Disease that were influenced by both the genetic factors and environmental factors. They all play important roles in disease pathogenesis.
   - Complicated disease, such as sporadic cancer
3. Disease that depends entirely on environmental factors
   - Nuclear radiation

Genetic marker

- **Complicated disease have genetic predisposition**
- **Genetic markers**
  - High penetrance genes
  - Single nucleotide polymorphism (SNP)
- **Genetic markers have two basic characteristics**
  - Heredity
  - Identifiability.

Single nucleotide polymorphism (SNP)

- **SNP is a variation in a single nucleotide that occurs at a specific position in the DNA.**
- **SNPs have no observable impact on the phenotype.**
- **It just influence the predisposition.**



Smoking and Lung cancer

- Tobacco smoke contains more than 4000 compounds, most of which are carcinogenic substance.
  - Particles：nicotine, PAHs (Polycyclic Aromatic Hydrocarbons), nitrosamine, et al.
  - Aerosol：carbon monoxide, benzene, acrolein, et al.
- Mechanism of tobacco carcinogenesis
  - Induce DNA damage——accumulation of harmful gene mutation——induce cancer
- Research by Hammond team：

Smoking per day：	**10-20** cigarettes	**20-40** cigarettes
The lung cancer mortality (smoker Vs non-smoker)	8.4 times	18 times

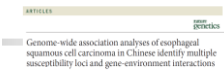
The probability of lung cancer in smokers was 10-20%

?

Hereditary susceptibility to lung cancer

- **Polymorphism (SNP) in metabolic enzyme gene**
  - CYPA1 activates some chemical substances in tobacco, such as polycyclic aromatic hydrocarbons, to form active carcinogens.
  - CST, coding the detoxifying enzyme, helps excrete toxic metabolite by catalyzing it to form combination with glutathione.

Drinking and Esophageal Cancer (ESCC)


Genome-wide association analyses of esophageal squamous cell carcinoma in Chinese identify multiple susceptibility loci and gene-environment interactions

Nat Genet. 2012 Oct;44(10):1090-7.

1、Risk lifestyle: **drinking**

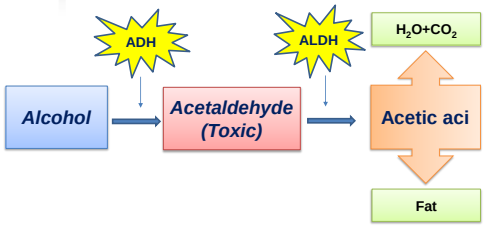
2、Risk genotype: ADHB1(G/**A**) and ALDH2(G/**A**)

3、Interaction between alcohol use and genetic variation

genotype		lifestyle	ESCC risk
• Non-risk genetic marker (G)	+	non-drinking	reference
• Non-risk genetic marker (G)	+	**drinking**	1.15 times
• Risk genetic marker (**A**)	+	non-drinking	1~1.4 times
• Risk genetic marker (**A**)	+	**drinking**	2.2~4.5 times

It is important for individuals carrying high-risk alleles to reduce alcohol use.

Alcohol-metabolizing pathway



Precision Prediction

(1) Primary prevention

(2) Secondary prevention

- Facilitating the stratification of susceptibility that help to guide timing and intensity of screening programs and avoid overscreening.

Hereditary breast-ovarian cancer syndrome (HBOC)

- Mother died from breast cacer at age 56, with a BRCA1 mutation
- She carries the same BRCA1 mutation
- 80% risk for breast cancer and a 50% risk for ovarian cancer
- At age 37, opted for mastectomy
- Raise public awareness for genomic testing and prevention

Screening program for Lynch Syndrome(HNPCC)

German HNPCC Consortium recommends Screening Program for Lynch Patients:

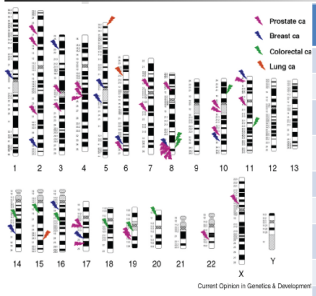
◆ Annual screening (age 25 onwards or beginning no later than 5 years before the lowest age of onset in family):

- Physical examination
- Abdominal ultrasound
- Full colonoscopy
- Gastroscopy (age 35 onwards)
- Gynecological examination including transvaginal ultrasound
- Endometrial pipelle biopsy (age 35 onwards)

Hereditary cancer syndrome

Disease	Gene	Related cancer	Risk
Hereditary breast-ovarian cancer syndrome (HBOC)	BRCA1, BRCA2	Breast cancer	BRCA1 mutation: 44-78%; BRCA2 mutation: 33-54%
		Ovarian cancer	BRCA1 mutation: 18-54%; BRCA12 mutation: 4%-18%
Lynch Syndrome, / Hereditary Non-Polyposis Colorectal Cancer （HNPCC）	MLH1,MSH2, MSH6,PMS2, ECAP	Colorectal cancer, endometrial cancer, gastric cancer, ovarian cancer,	Colorectal cancer: 52-82% endometrial cancer: 25-60% gastric cancer: 6-13% ovarian cancer: 4%-12%
Familial adenomatous polyposis （FAP）	APC	Colorectal cancer, Colorectal adenomatous polyposis	100%
Hereditary diffuse gastric cancer,(HDGC)	CDH1	Gastric cancer	Men：67% Women：83%

Sporadic cancer related risk SNP



Cancer type	Associated SNP
Prostate cancer	103
Breast cancer	125
Colorectal cancer	41
Esophageal cancer	27
Lung cancer	18
Bladder cancer	14
Pancreatic cancer	11
Glioma	9
Thyroid cancer	7

Genetic risk score

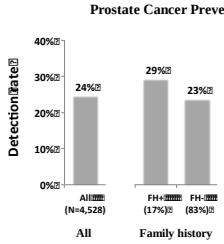
- Each SNP has modest effect size

- Multiple SNPs confer a stronger effect to disease

Genetic risk score (RGS)

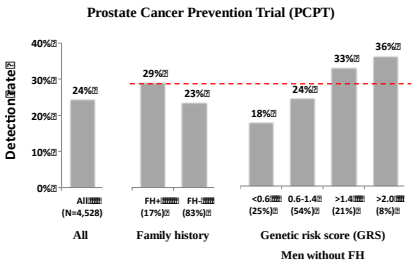
- **Based on multiple disease risk-associated SNPs, and weighted by their effect.**

Stratification of Susceptibility



Stratification of Susceptibility

Genetic risk score: based on risk-associated genotype



New PSA Guidelines Discourage Overscreening

Judy Peres

J Natl Cancer Inst (2012) 104 (1): 8-9. DOI: https://doi.org/10.1093/jnci/djr539
Published: 04 January 2012

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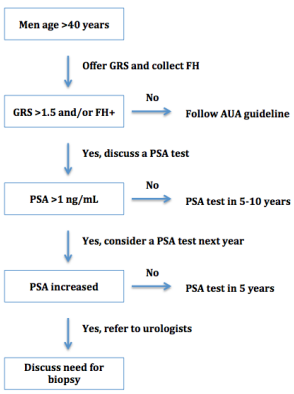
The new prostate cancer screening recommendation that the U.S. Preventive Services Task Force issued in October provoked the predictable firestorm of controversy between proponents of early detection and critics who believe many screening tests have been overpromoted. But the reaction was more muted than expected, leading some to suggest that the pendulum might be swinging away from routine screening.

- Risk for prostate cancer
  - Family history
  - PSA level : Low-risk: PSA<6; Intermediate-risk: PSA10-20; High-risk: PSA>20
- Only 30% of patients with high PSA have prostate cancer diagnosed after biopsy.
- Nearly 90% of men with PSA-detected prostate cancer undergo early treatment with surgery, radiation, or androgen-deprivation therapy.



Precision Prediction

(1) Primary prevention

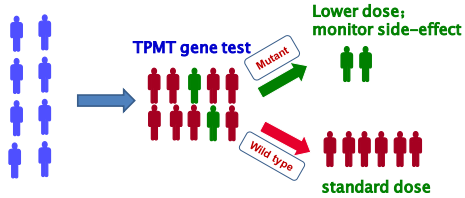
(2) Secondary prevention

(3) Tertiary prevention

- Aiding the prognosis that help to establish appropriate clinical treatment decision and cancer management strategy.

Prognosis of treatment response

- Purine is a anti-tumor drug
- When given the standard dose of purine drugs, patients with TPMT deficiency suffered from severe toxicity.



How precision prediction might work ?

The answer:

(1) helping to predict a person's susceptibility to adverse lifestyle exposures.

(2) facilitating the stratification of susceptibility that help to guide timing and intensity of screening programs and avoid overscreening.

(3) aiding the prognosis that help to establish appropriate clinical treatment decision and cancer management strategy.

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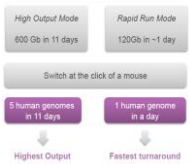
- **The ethic of genetic testing**

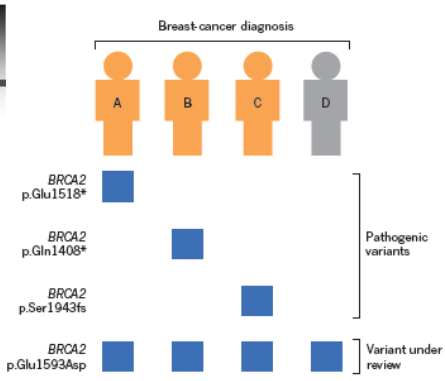
The widespread use of Next generation sequencing (NGS) technology

1990年-2005年
Human Genome Project
- 13 years
- 3.8 billion dollars

2008年
The first individual genome sequencing was finished using the NGS
- 2 month
- about 1 million dollars

Now
Developed NGS
- 1day
- 1 thousands dollars





Discussion

- **Returning results:**
  Genome sequencing producing massive amounts of data of unknown medical and social impact.
  - Return information about actionable results
  - Patients want information about all findings from sequencing
- **Privacy and confidentiality**
  - Patients do not want their sequencing results 'filtered'
  - New technology need data sharing to achieve common standards for analytical validity, different testing platforms.
- **Personal genetic testing:**
  - In 2013, the FDA directed 23andMe to cease selling Personal Genomic Testing (PGS) kits.
  - In February 2015, the FDA reclassified these kits to enable a regulatory path exempt from premarket review.

Thanks !