The Royal Melbourne Hospital

THE UNIVERSITY OF MELBOURNE

Genetics and Genomics in General Practice: Breast and Colorectal Cancer

Professor Ingrid Winship

Melbourne, October 2018

Transition from genetics to genomics

Genetics is the study of heredity.

Genomics is the study of genes and their functions, and related techniques.

Genetics scrutinizes functioning/ composition of the single gene

whereas

Genomics addresses all genes and their inter relationships

The uses of genomic DNA

- Diagnostic confirmation
- Predicting risks- carriers
  - -presymptomatic
  - -predisposition
  - -polygenic risk score
- Prenatal/ preimplantation tests
- Intervention- pharmacogenomics
  - - gene based therapy

Whole genome sequencing (WGS):
3.3 billion bp
Whole exome sequencing (WES):
10 million bp

Target age group?

Prenatal

Paediatric

Reproductive
pre-conception

(paternity)

Pharmacogenomics

Adult-onset

Forensic

The value of a diagnosis

- Diagnostic odyssey
- Planning
- Resources…..

What is precision medicine?

- An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.*https://ghr.nlm.nih.gov/primer/precisionmedicine/definition (accessed 2017)*
- The correlation of innate and external factors at an individual level, to better understand the pattern of disease and its impact on that individual and thus to tailor prevention, intervention and treatment. *Winship I Med J Aust. 2015. 203(3):132-3*
- "4P Medicine- predictive, personalised, preventive and participatory." *Hood, L &Friend S. Nature Reviews Clinical Oncology 2011. 8: 184-187*

What is penetrance?

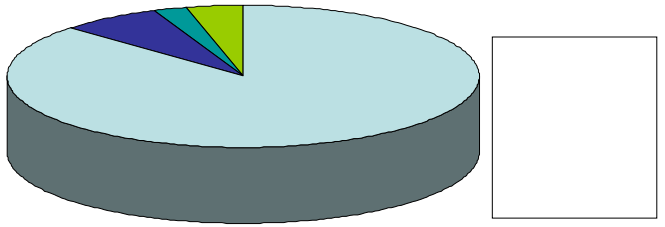
- the extent to which a particular gene or set of genes is expressed in the phenotypes

- the proportion of carriers showing the characteristic phenotype.

Mechanisms which confer resilience??

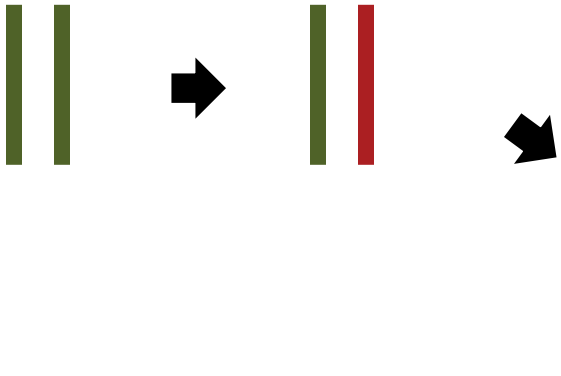
Inherited Predisposition to cancer

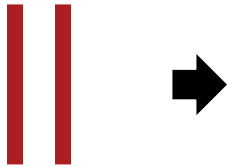
- MANY CLOSE RELATIVES
- SUCCESSIVE GENERATIONS
- YOUNG PEOPLE
- BILATERAL/MULTIPLE TUMOURS (synchronous or metachronous)
- CONSTELLATIONS: BREAST AND OVARY
- TUMOUR CHARACTERISTICS:TRIPLE NEGATIVE



Double hit hypothesis

Sporadic cancer
2 acquired mutations





Tumour formation

Hereditary cancer
1 inherited
1 acquired mutation

Accurate assignment of pathogenicity of variants:

- Confirms clinical diagnosis
- Optimises individual management
- Allows predictive testing
- Optimises family management
- Allows prenatal or pre-implantation genetic diagnosis
- Optimises reproductive options
- Allows pharmaco-genomic testing
- Optimises pharmacologic management

Genetic factors that contribute to cancer: key knowledge points

- High risk genes
- Moderate risk genes
- Polygenic risk
- Genetic testing, eligibility and its utility

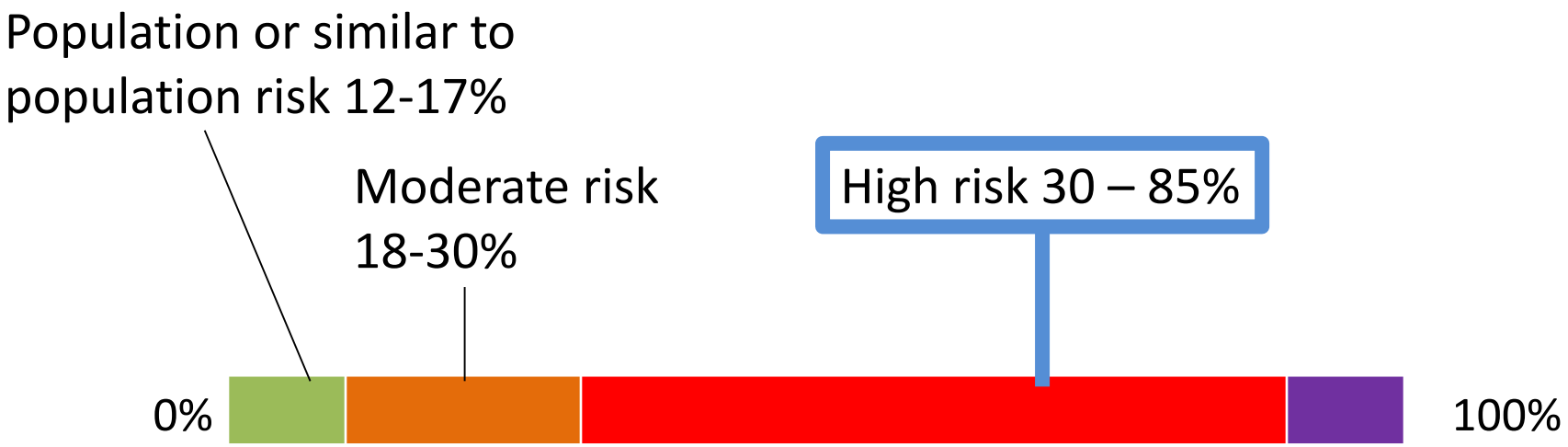
Breast cancer risk genes

All women and all men have two copies of these genes, inherit one from each parent

Genes mainly code for proteins involved in DNA repair

When there are changes that prevent the normal function of the protein ie pathogenic variant or mutation this change in the gene is associated with an increased lifetime breast cancer risk

High risk genes



Lifetime risk of developing breast cancer

High risk genes – *BRCA1*

Women

Increased breast and ovarian cancer risk

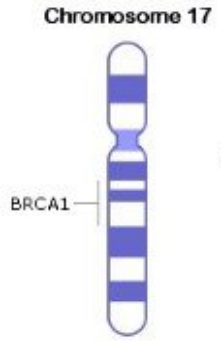
Breast cancer risk increases around ages 25-30

Ovarian cancer increases around age 40

Men

Small risk of male breast cancer

A <u>potential</u> increase in prostate cancer risk



National Library of Medicine, NCBI

High risk genes – *BRCA2*

Women

Increased breast and ovarian cancer risk

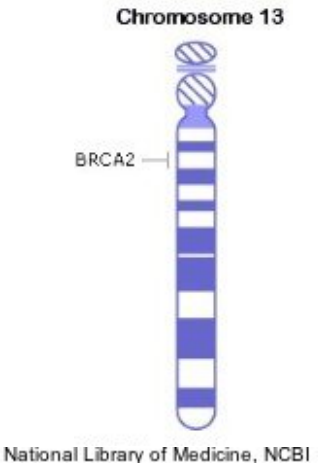
Breast cancer risk increases around age 30

Ovarian cancer increases around age 45

Men

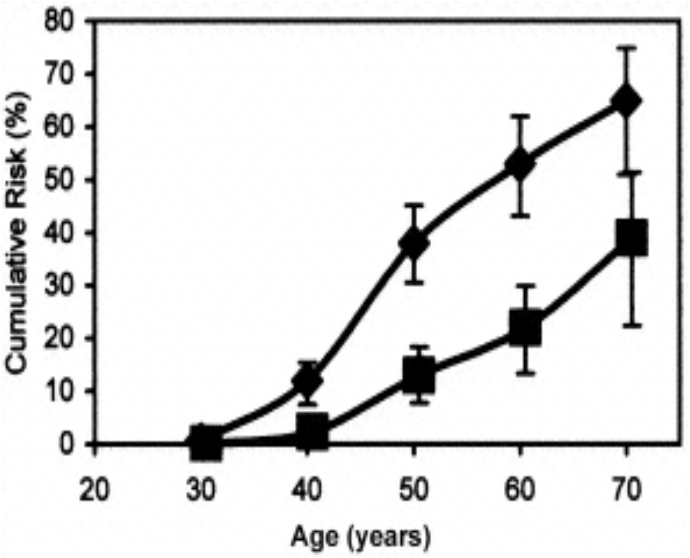
Small risk of male breast cancer

Increased prostate cancer risk around age 45

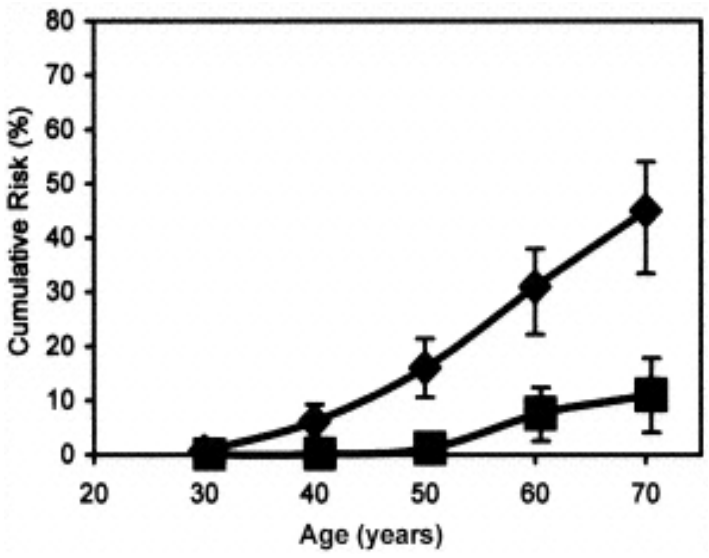


Men and women have a slightly higher risk of developing pancreatic cancer and melanoma

BRCA1 risk



BRCA2 risk



Antoniou et al 2003

High risk genes – *PALB2*

Women

Increased breast cancer risk

Breast cancer risk increases around age 30

Pancreatic cancer risk may be increased

Men

Currently no male specific cancer risks identified

PALB2 effect variable in different families: may conveys a high risk or a moderate risk

High risk genes – *TP53*

Li-Fraumeni syndrome

Women

Increased breast cancer risk

Breast cancer risk increases around age 20

Both **men** and **women** have a high risk of developing other types of cancers including sarcoma.

High risk genes – *Others*

*PTEN (*Cowden syndrome*)*

Increased risk of breast, thyroid & endometrial cancer

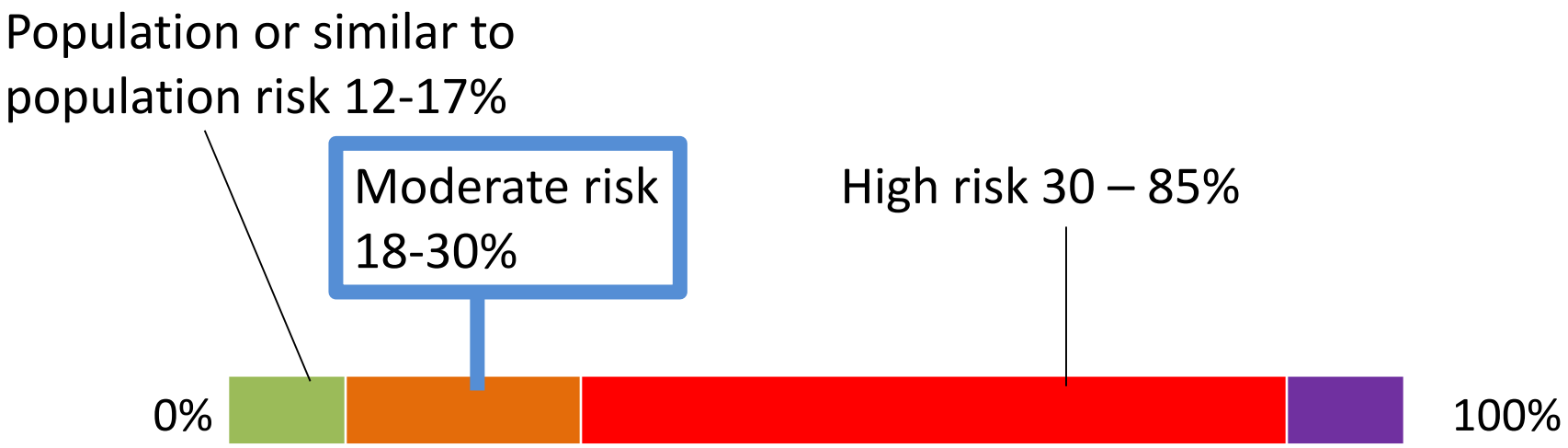
*CDH1 (*Hereditary diffuse gastric cancer*)*

Increased risk of lobular breast cancer and diffuse gastric cancer

*STK11 (*Peutz-Jeghers syndrome*)*

Increased risk of breast, pancreatic and GI cancers

Moderate risk genes



Lifetime risk of developing breast cancer

Moderate risk genes – *CHEK2*

Women

Increased breast cancer risk

c.1100delC variant

high breast cancer risk in some families

Other variants

Insufficient data to determine penetrance and surveillance accurately so base on family history

Moderate risk genes – *ATM*

Women

Increased breast cancer risk

c.7271T>G variant

seems to be similar risk to *BRCA2*

Other variants

Insufficient data to determine penetrance and surveillance accurately so base on family history

SNPs
(Single Nucleotide Polymorphisms)

- Common single base differences between individuals in the DNA sequence (the inherited DNA, not tumour DNA)
- Humans have millions of these SNPs.
- Most SNPs have no effect on function, but others could predispose people to disease

Polygenic risk scores

- Combinations of SNPs (single nucleotide polymorphisms)
- Small effect sizes, cumulative effect
- In the right combination and with/without a high/moderate risk breast cancer gene this can influence an individuals lifetime risk of developing breast cancer

Gene Panels, WES and WGS

- Traditional iterative approach to testing has poor diagnostic yield
- Heterogeneity – many genes
- Expensive
- Syndromes overlap
- Can test multiple genes simultaneously

Genetic Testing

BRCA PLUS Panel - *BRCA1, BRCA2, PALB2, TP53* & *ATM* (c.7271T>G)

Medicare funded testing (Nov, 2017)

- Specialist/consultant physician can order for patients with breast (or ovarian) cancer
- PHx Breast Ca BOADICEA score ≥10% or Manchester score ≥16

Item 73295	**Detection of germline BRCA1 or BRCA2 gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer, with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme are fulfilled. Maximum of one test per patient's lifetime**
Item 73296	Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in BRCA1 and BRCA2 genes and one or more of the following genes STK11, PTEN, CDH1, PALB2, or TP53 in a patient with breast or ovarian cancer for whom clinical and family history criteria, as assessed by the specialist or consultant physician who requests the service using a quantitative algorithm, place the patient at > 10% risk of having a pathogenic mutation identified in one or more of the genes specified above.
Item 73297	Characterisation of germline gene mutations, requested by a specialist or consultant physician, including copy number variation in BRCA1 and BRCA2 genes and one or more of the following genes STK11, PTEN, CDH1, PALB2, or TP53 in a patient who is a biological relative of a patient who has had a pathogenic mutation identified in one or more of the genes specified above, and has not previously received a service under item 73296.

Source: Medicare Benefits Schedule Online (http://www9.health.gov.au/mbs/search.cfm).

Mainstreaming services at Parkville

- Who can request: Medical specialist following formal arrangement and a quick training session)
- Rationale:result will inform treatment
- Triple negative <60, invasive carcinoma ≤35, male Breast Ca
- Result is given by treating clinician. If pathogenic mutation identified or significant family history, referred to FCC
- 8 week TAT but can be 2 week TAT with BRCA1/2 only by special request with the lab

INTERVENTIONS

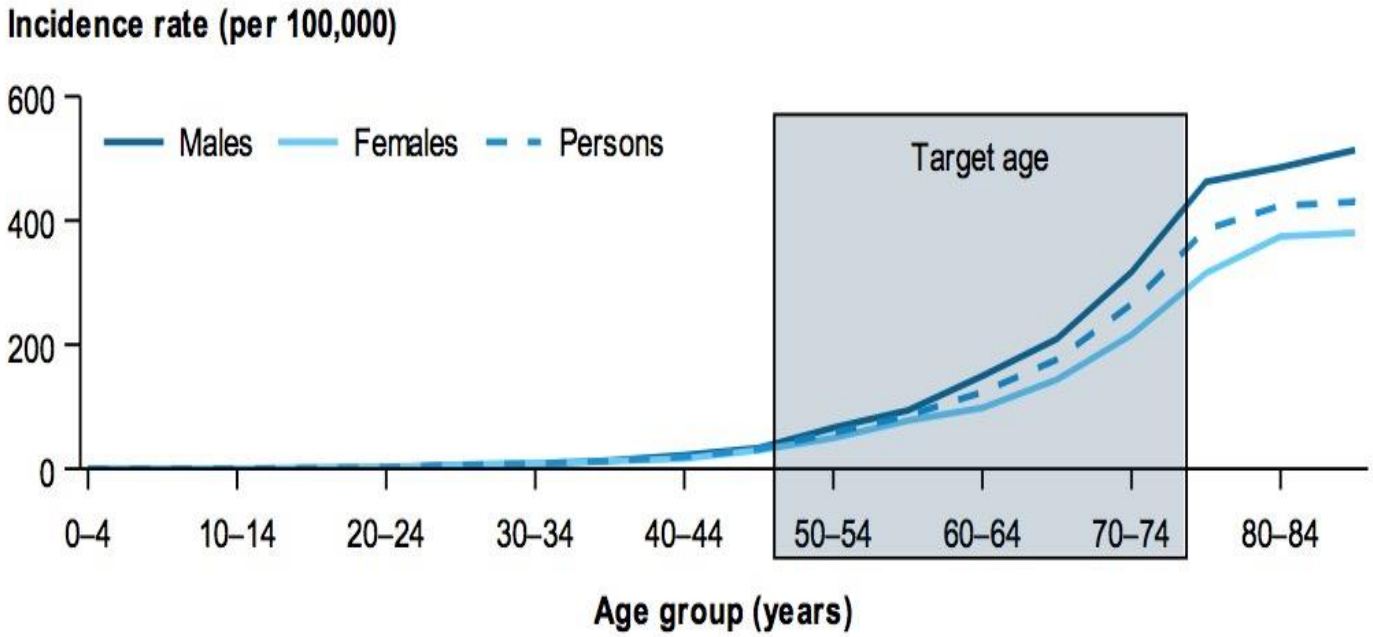
- Lifestyle
- Cancer surveillance
- Risk reduction surgery
  - BSO, BPM
- Chemoprevention-Tamoxifen
- Targeted therapy-PARPi

- Release from screening for those found not to be at high risk

Colorectal cancer

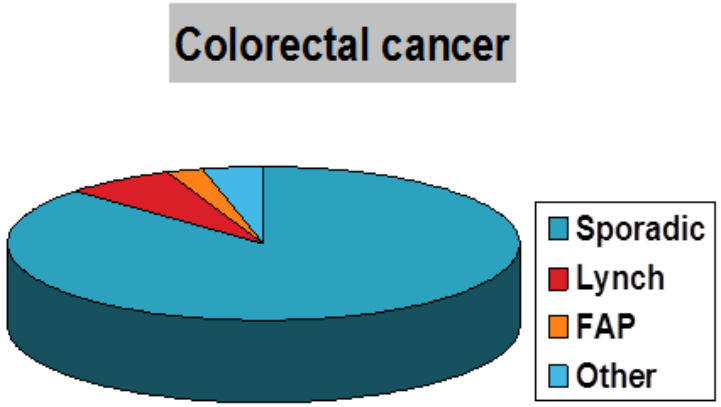
- Colon and rectum = colorectum (bowel)
- 1 in 15 will develop cancer of the colorectum
- 30-40% of these will die from their disease
- Most colorectal cancer starts from a precursor benign lesion (polyp or adenoma)

- Detection and removal of polyp prevents cancer
- Detection and treatment at an early stage greatly reduces risk of death



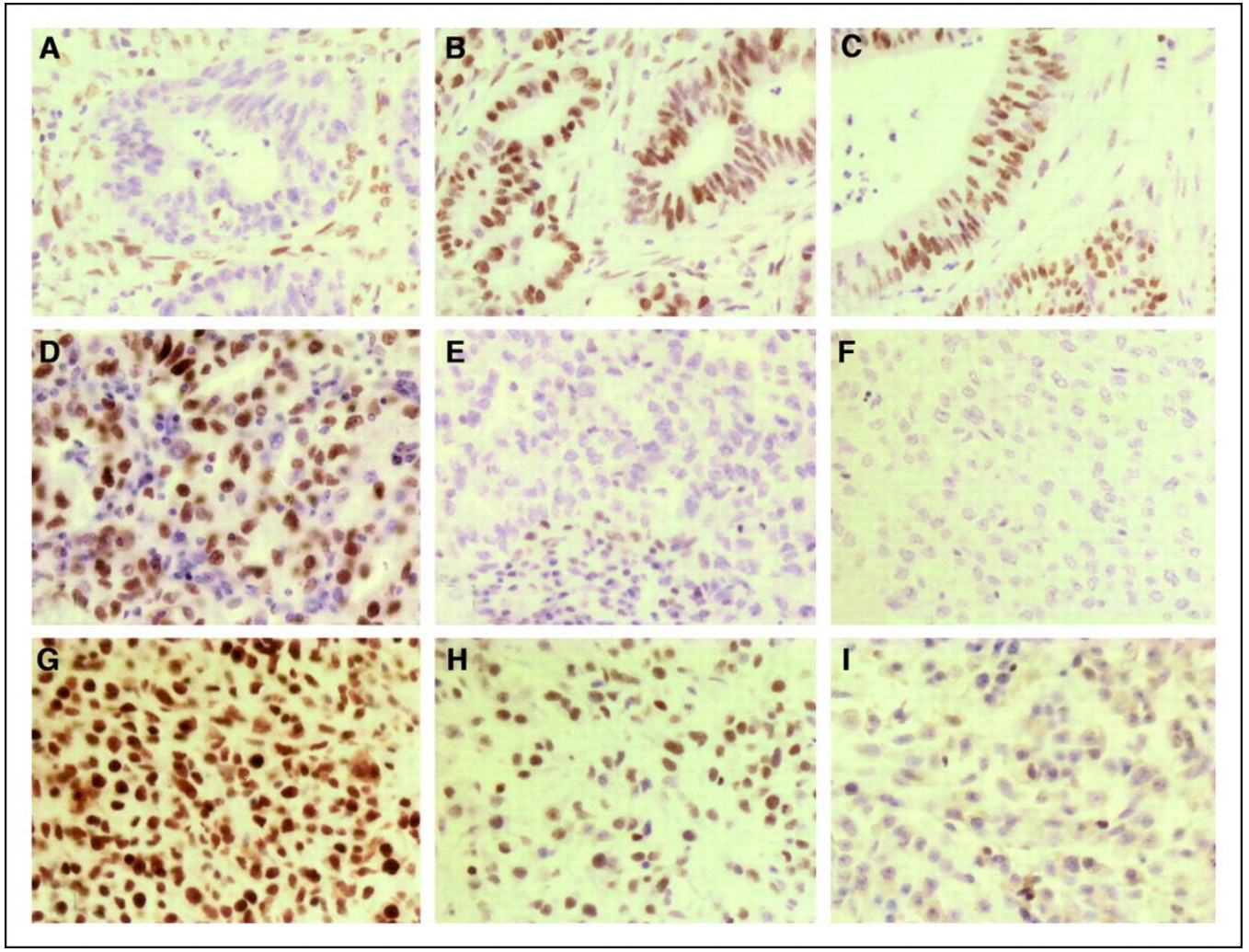
Australian Institute of Health and Welfare 2017. National Bowel Cancer Screening
Program: monitoring report 2017. Cancer series no.104. Cat. no. CAN 103. Canberra: AIHW.

Inherited Predisposition to Colorectal Cancer



- MANY CLOSE RELATIVES
- SUCCESSIVE GENERATIONS
- YOUNG PEOPLE
- BILATERAL/MULTIPLE TUMOURS (synchronous or metachronous)
- POLYPS
- CONSTELLATIONS: CRC and UTERINE
- TUMOUR CHARACTERISTICS: IHC

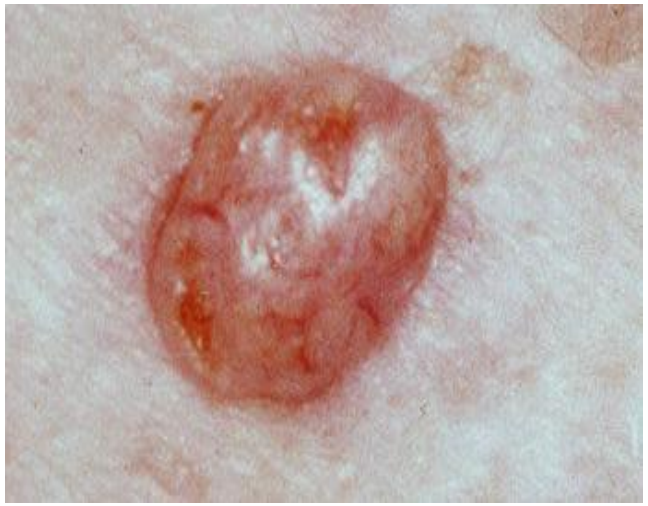
IMMUNOSTAINING IN COLON CANCER (MLH1 mutation)

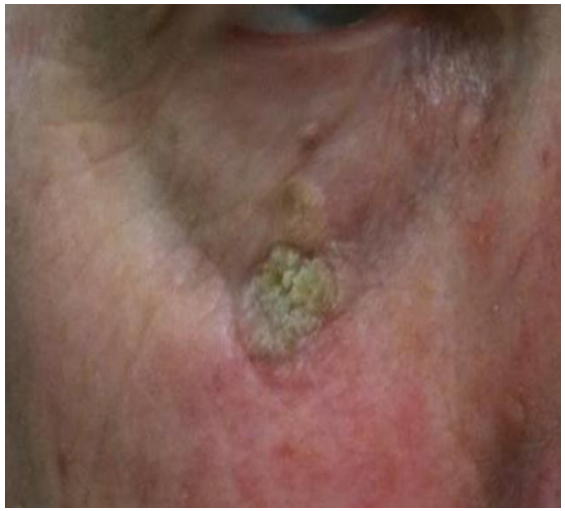


Stormorken, A. T. et al. J Clin Oncol; 23:4705-4712 2005

Sebaceous skin lesions:

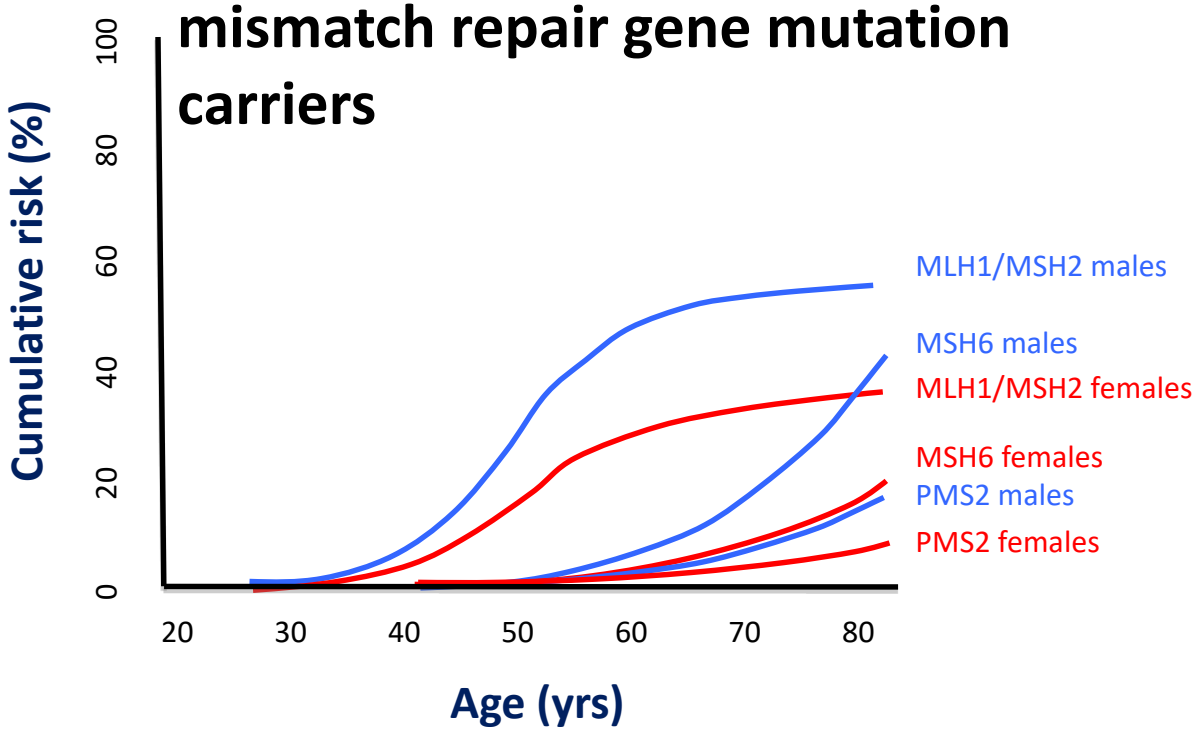
Adenoma
Carcinoma





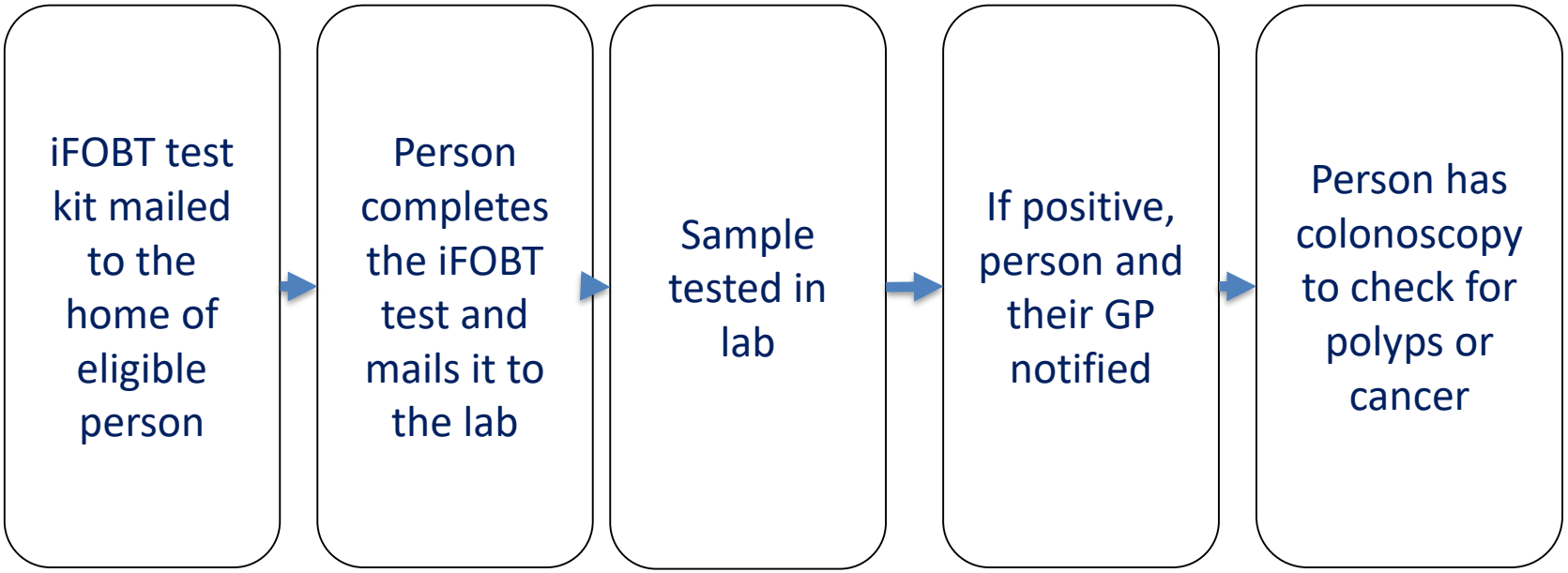
Muir Torre Syndrome vs Lynch Syndrome?

Risk of colorectal cancer for DNA mismatch repair gene mutation carriers



Hopper 2011

National Bowel Cancer Screening Program



NATIONAL BOWELCANCER SCREENING PROGRAM

Participation = 38%

l screening from age

ectal

Screening is $30) and avoids expensive c orectal cancer treatment ($36,000-$73,00)

An increase of just 10% in screening participation will prevent an additional 24,000 deaths over 25 years and decrease health systems expenditure by $300 million.

Lew et al. Lancet Public Health, 2017

Our research:
Determine ways to increase screening effectiveness using a risk-based approach (precision public health)

2017 Colorectal Cancer Screening Guidelines

Risk categories	Near average risk	Moderately increased risk	High risk (excludes Lynch syndrome)
Definition of Family history	No FDR with CRC Or One FDR with CRC over 55	One FDR with CRC before 55 Or Two FDRs with CRC diagnosed over 55	Stronger family history
Relative risk	1-2	3-6	7-10
Screening	iFOBT every 2 years from age 50	iFOBT every 2 years from age 40 then colonoscopy every 5 years from 50	iFOBT every 2 years from age 35 then colonoscopy every 5 years from age 45

SNPs
(Single Nucleotide Polymorphisms)

- Common single base differences between individuals in the inherited DNA sequence
- Humans have millions of these SNPs.
- Most SNPs have no effect on function, but others or combinations could predispose people to disease
- **At least 45 of them are associated with colorectal cancer risk.** (Jenkins et al, Future Oncology 2016)

SNPs from published studies that are associated with colorectal cancer risk

N=45

Average odds ratio per risk allele 1.14 (range: 1.05–1.53).

Account for 22% of the total familial relative risk

Locus&	SNP&	Nearest&gene(s)&	OR&per&risk& allele*&	freq&of& risk& allele&	proportion&of& FRR[#]&
1p36.2&	rs72647484(	*WNT4;&CDC42&*	1.21(	0.91(	0.37%(
1q25.3&	rs10911251(	*LAMC1&*	1.05(	0.54(	0.07%(
1q41&	rs6687758(	*DUSP10;&LOC729082;&PCP13&*	1.09(	0.2(	0.15%(
2q32.3&	rs11903757(	*NABP1;&MYO1B;&SDPR&*	1.06(	0.36(	0.37%(
3p14.1&	rs812481(	*LRIG1&*	1.09(	0.58(	0.22%(
3p22.1&	rs35360328(	*RP11;&CTNNB1&*	1.14(	0.16(	0.29%(
3q26.2&	rs10936599(	*MYNN;&TERC&*	1.08(	0.75(	0.14%(
4q26&	rs3987(	*NDST3&*	1.36(	0.44(	2.87%(
4q32.2&	rs35509282(	*FSTL5&*	1.53(	0.09(	1.83%(
5q31.1&	rs647161(	*PITX1;&H2AFY&*	1.11(	0.67(	0.30%(
6p21.31&	rs1321311(	*CDKN1A&*	1.1(	0.23(	0.20%(
8q23.3&	rs16892766(	*EIF3H&*	1.25(	0.07(	0.40%(
8q24.21&	rs6983267(	*CCAT2;&MYC&*	1.21(	0.52(	1.12%(
9q24&	rs719725(	*TPD52L3;&UHRF2&*	1.19(	0.37(	0.13%(
10p13&	rs10904849(	*CUBN&*	1.14(	0.68(	0.46%(
10p14&	rs10795668(	*GATA3&*	1.12(	0.67(	0.35%(
10q22.3&	rs704017(	*ZMIZ1;&AS1&*	1.06(	0.57(	0.10%(
10q24.2&	rs11190164(	*SLC25A28;&ENTPD7;&COX15;&CUTC;&ABCC2&*	1.09(	0.29(	0.19%(
10q25&	rs12241008(	*VTI1A&*	1.13(	0.09(	0.15%(
11q12.2&	11qhap^(	*FADS1;&FEN1&*	1.4(	0.57(	3.41%(
11q13.4&	rs3824999(	*POLD3&*	1.08(	0.5(	0.18%(

(

Locus!	SNP!	Nearest-gene(s)!	OR-per-risk-allele*!	freq-of-risk-allele!	proportion-of-FRR[#!]
11q23.1-	rs3802842!	*COLCA2&*	1.11!	0.29!	0.28%!
12p13.32-	rs3217810!	*CCND2&*	1.2!	0.16!	0.55%!
12p13.32-	rs3217901!	*CCND2&*	1.1!	0.41!	0.27%!
12p13.32-	rs10774214!	*CCND2&*	1.09!	0.38!	0.22%!
12q13.13-	rs11169552!	*DIP2B;&ATF1&*	1.09!	0.72!	0.18%!
12q13.13-	rs7136702!	*LARP4;&DIP2B&*	1.06!	0.35!	0.10%!
12q24.12-	rs3184504!	*SH2B3&*	1.09!	0.53!	0.23%!
12q24.21-	rs59336!	*TBX3&*	1.09!	0.48!	0.23%!
12q24.22-	rs73208120!	*NOS1&*	1.16!	0.11!	0.26%!
14q22.2-	rs1957636!	*BMP4&*	1.08!	0.4!	0.18%!
14q22.2-	rs4444235!	*BMP4&*	1.11!	0.46!	0.33%!
15q13.3-	rs11632715!	*SCG5;&GREM1&*	1.12!	0.47!	0.39%!
15q13.3-	rs16969681!	*SCG5;&GREM1&*	1.18!	0.09!	0.28%!
16q22.1-	rs9929218!	*CDH1&*	1.1!	0.71!	0.23%!
16q24.1-	rs16941835!	*FOXL1&*	1.15!	0.21!	0.40%!
17q21-	rs744166!	*STAT3&*	1.27!	0.55!	1.74%!
18q21.1-	rs4939827!	*SMAD7&*	1.18!	0.52!	0.84%!
19q13.11-	rs10411210!	*RHPN2&*	1.15!	0.9!	0.22%!
19q13.2-	19qhap^!	*TMEM91;&TGFB1&*	1.16!	0.49!	0.68%!
20p12.3-	rs2423279!	*FERMT1;&BMP2&*	1.14!	0.3!	0.44%!
20p12.3-	rs4813802!	*FERMT1;&BMP2&*	1.09!	0.36!	0.21%!
20p12.3-	rs961253!	*FERMT1;&BMP2&*	1.12!	0.36!	0.36%!
20q13.1-	rs6066825!	*PREX1&*	1.09!	0.64!	0.21%!
20q13.33-	rs4925386!	*LAMA5&*	1.08!	0.68!	0.16%!

!

Jenkins et al, Future Oncology 2016

Advantages of using SNPs

- Inexpensive and accurate
- Growing public acceptance for private/personalised genomic tests
- Easy to provide DNA (saliva or cheek swab)
- Does not have same implications for family members as single genes

Disadvantages of using SNPs

- Insurance issues not clear
- Need introduction to health system

- Current SNPs are at least as important as family history for assessment of colorectal cancer risk

- SNPs can be use to identify high- and low-risk people, especially in familial cancer clinic settings

- In combination, family history and SNPs can be use to identify high- and low-risk segments of the population and therefore risk-based population screening is worth investigating.

Genes translate to aid a preventive approach to clinical management

Individual

- Diagnosis
- Risk assessment
  - Family history
  - Age of onset
  - Constellation of signs and symptoms
  - Diagnostic tools- pathology
  - Mutation detection
- Management- targeted therapy
- Pharmacogenomics
- Ongoing risk management
- Reproductive options
- Evidence based strategies
- Counselling and Advocacy

Family members

Risk Assessment

- Family history
- Predictive testing

Risk Management-**<u>evidence based</u>**

- Surveillance
- Surgery
- Intervention
- Chemoprevention

Reproductive options

Counselling and Advocacy

What is precision medicine?

- The correlation of innate and external factors at an individual level, to better understand the pattern of disease and its impact on that individual and thus to tailor prevention, intervention and treatment. *Winship I Med J Aust. 2015. 203(3):132-3*

Precision medicine

- Effective diagnosis
- Effective treatment
- Effective prevention

Effective diagnosis- lifelong selective analysis

Germline

- Panels testing
- WES
- WGS

Somatic

- Tumour testing

Informatics, curation of variants

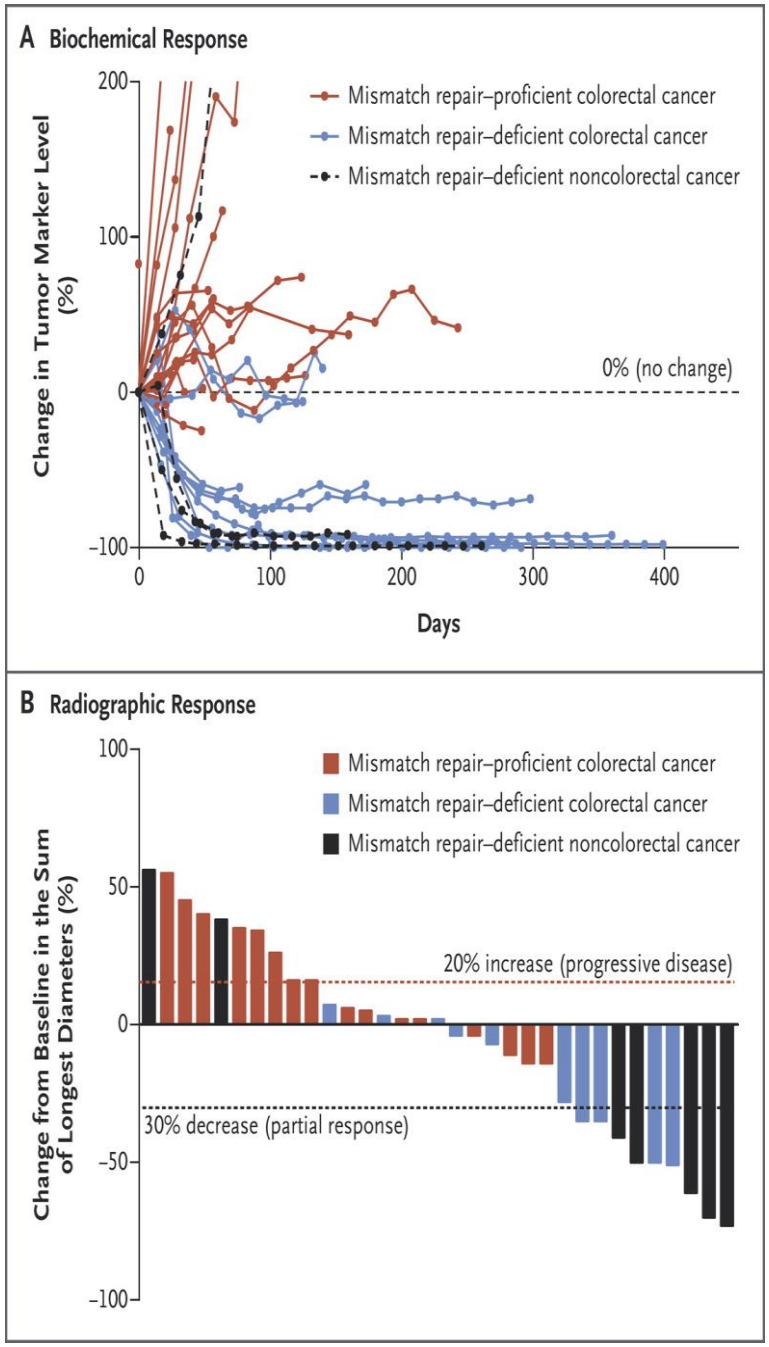
Polygenic risk scores

Assigning pathogenicity: clinical implications

- CLASS 5: Pathogenic mutation. Predictive testing available to family members, including prenatal diagnosis.
- CLASS 4: Likely pathogenic mutation. Predictive testing is available to other family members in conjunction with clinical screening.
- CLASS 3a:Variant of unknown significance (VUS) with high clinical significance. Co-segregation studies in family members is strongly recommended to determine pathogenicity. Predictive testing is **NOT** available to family members.
- CLASS 3b: Variant of unknown significance (VUS). Co-segregation studies in family members may help clarify pathogenicity. Predictive testing **NOT** available to family members.
- CLASS 3c: Variant of unknown significance (VUS) with low clinical significance. Co-segregation studies in family members may help clarify pathogenicity. Predictive testing **NOT** available to family members.

Accurate assignment of pathogenicity of variants:

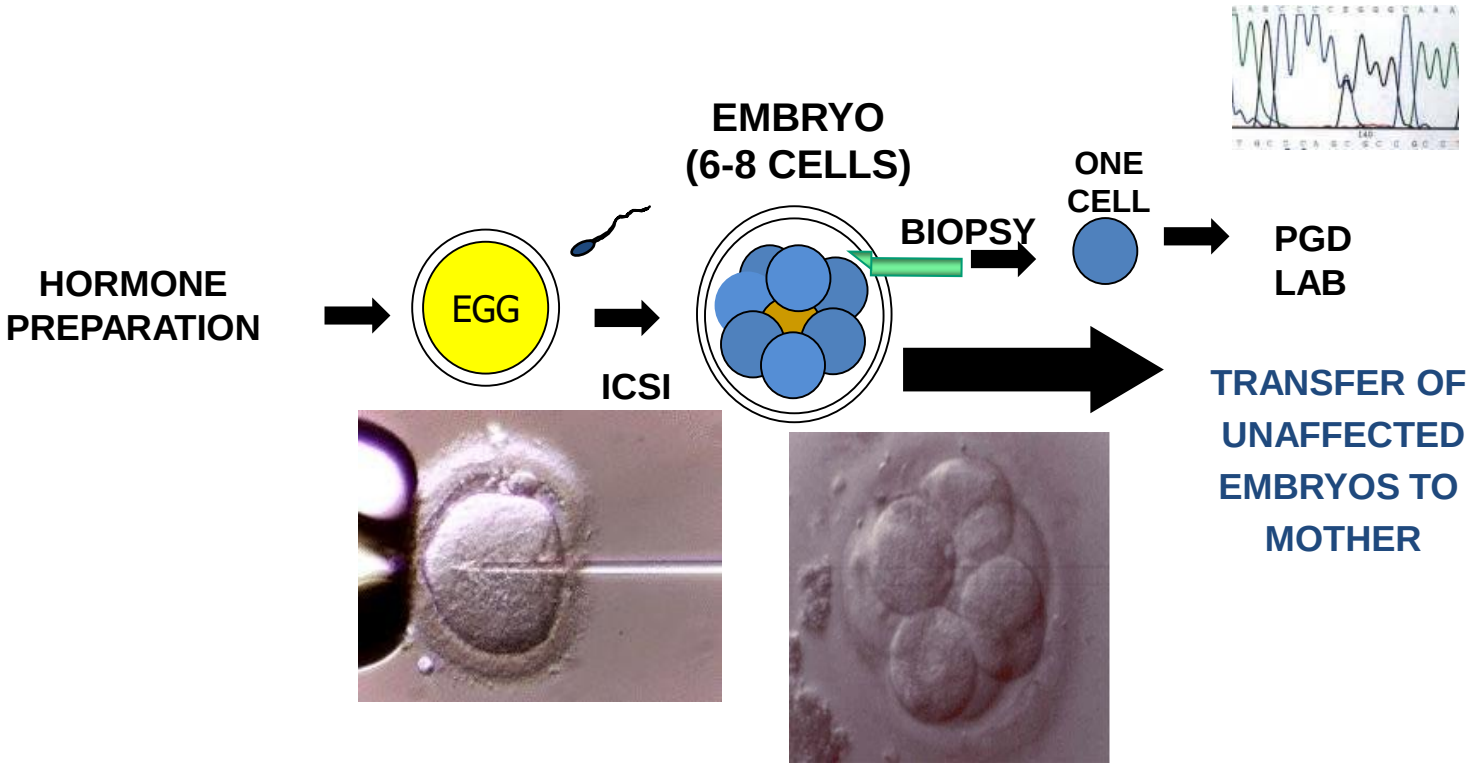
- Confirms clinical diagnosis
- Optimises individual management
- Allows predictive testing
- Optimises family management
- Allows prenatal or pre-implantation genetic diagnosis
- Optimises reproductive options
- Allows pharmaco-genomic testing
- Optimises pharmacologic management



Mismatch-repair status predicted
benefit of immune
checkpoint blockade with pembro

Le D et al N Engl J Med 2015; 372:2509-2520

PRE-IMPLANTATION GENETIC DIAGNOSIS



Multidisciplinary teams

CORE CLINICAL STAFF

- GENETIC COUNSELLORS
- CLINICAL GENETICISTS
- NURSES
- DATA MANAGEMENT
- ADMINISTRATION/LOGISTIC

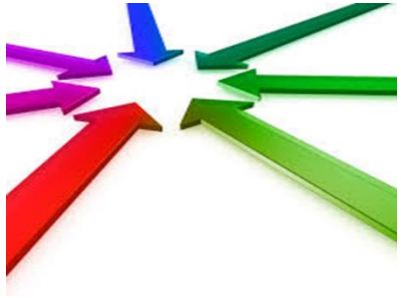
CONTENT EXPERTS

- MED ONC- HBOC
- CARDIOLOGIST/ELECTROPHYSIOLOGIST
- GASTROENTEROLOGIST-CRC
- NEUROLOGIST
- IMMUNOLOGIST
- NEPHROLOGST/ UROLOGIST
- DERMATOLOGIST

CORE LABORATORY STAFF

- SCIENTISTS
- STATISTICIANS
- DATABASE CURATORS
- MOLECULAR PATHOLOGISTS
- BIO-INFORMATICIANS
- CURATION

COLLABORATION



The uses of genomic DNA, germline and somatic: underpins precision medicine

- Diagnostic confirmation
- Predicting risks- carriers
  - -pre-symptomatic
  - -predisposition
- Prenatal/ preimplantation/NIPT
- Polygenic risk scores
- Intervention- pharmacogenomics
  - - targeted therapies
  - - gene therapy
  - - gene editing
- Prognosis

What will precision medicine achieve?

- A focus on wellness -prevention
- Better health outcomes
- Less adverse events
- Less clinical waste
- Translation and implementation

of research into practice

Ethical and legal issues in genomics

- Interested third parties!
- WES and WGS
- Return of results
- Binning…according to utility
- What is medically actionable
- Consent from the start

ASHG: October 2018

High Polygenic Risk Score for Heart Disease Motivates Patients to Make Lifestyle Changes

The role of genomics to shape health care, towards precision medicine: Genomic Medicine @RMH.

- Early detection
- Early intervention
- Targeted therapy
- Preventing predictable disease
- Preventing predictable complications of disease
- Preventing predictable complications of treatment

Victorian Familial Cancer Centres

Austin Familial Cancer Centre

Austin Hospital, Heidelberg

- Provide regional service to Ballarat, Wodonga and Shepparton

Cabrini Health Familial Cancer Centre

Cabrini Health, Malvern

Monash Familial Cancer Centre

Monash Medical Centre, Clayton

- Provide regional service to Moe and Frankston

Parkville Familial Cancer Centre

Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Parkville

- Provide regional service to Bendigo, Mildura, Geelong and Warrnambool

Risk assessment and risk management

Individual

- Diagnosis
- Risk assessment
  - **Family history**
  - **Age of onset**
  - **Constellation of signs and symptoms**
  - **Diagnostic tools- pathology**
  - **Mutation detection**
- Management- targeted therapy
- Pharmacogenomics
- Ongoing risk management
- Reproductive options
- Evidence based strategies
- Counselling and Advocacy

Family members

Risk Assessment

- Family history
- Predictive testing

Risk Management-**evidence based**

- Surveillance
- Surgery
- Intervention
- Chemoprevention

Reproductive options

Counselling and Advocacy

If genetic testing to be done:

Pre Test Discussion

- Risks associated with mutations the relevant genes
- Management options
- Inheritance (implications for family members)
- Insurance

Post Test Discussion

- Risk management plan
- Adjustment to the result/ psychosocial support
- Sharing information with family members
- Predictive testing for family members
- Reproductive options
- Long term follow-up and support for carriers

Other resources

Cancer Australia: www.canceraustralia.gov.au

Cancer Council of Victoria (CCV): www.cancervic.org.au

EVIQ: www.eviq.org.au

Australian Government Cancer Screening Programs: www.cancerscreening.gov.au

Gene Based Strategies Informed by Translation of Research to Practice

- Early detection
- Early intervention
- Targeted therapy
- Preventing predictable disease
- Preventing predictable complications of disease
- Preventing predictable complications of treatment
- **Using genes to keep healthy people healthy!**