Ovarian Cancer Australia

Ovarian Cancer Australia Webinar "What is ovarian cancer"?

Ovarian cancer – how we are getting to know the enemy

Professor David Bowtell
Peter MacCallum Cancer Centre, Melbourne
Garvan Institute and Kinghorn Cancer Centre, Sydney
d.bowtell@petermac.org; d.bowtell@garvan.org.au

Talk outline

- Recognizing the different types of ovarian cancer
- Genes that influence the risk of developing ovarian cancer
- Genes that influence the response of the cancer to treatment
- The development of drug resistant cancers with therapy

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Cancer diagnosis has been based on location in the body and patterns of cell growth

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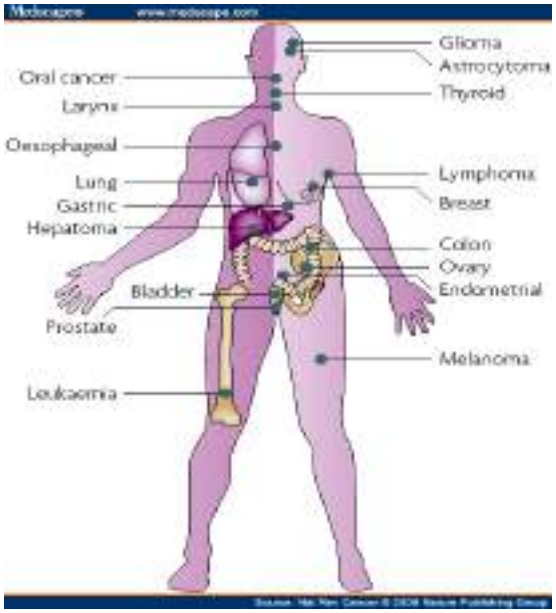
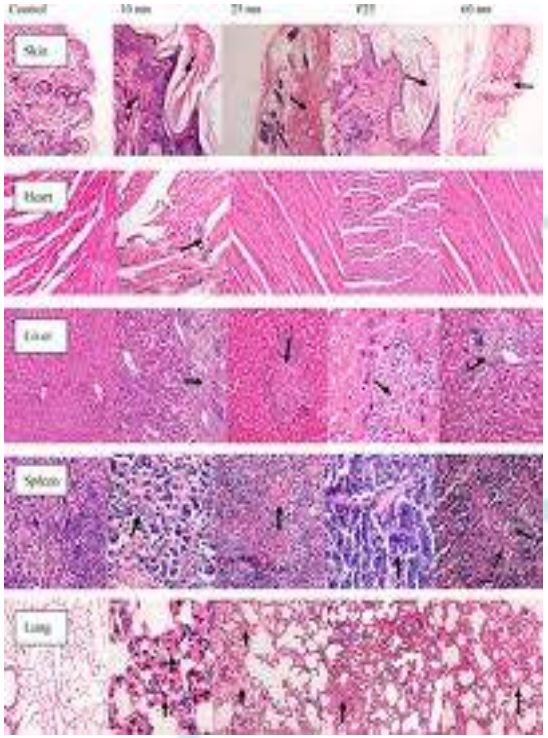
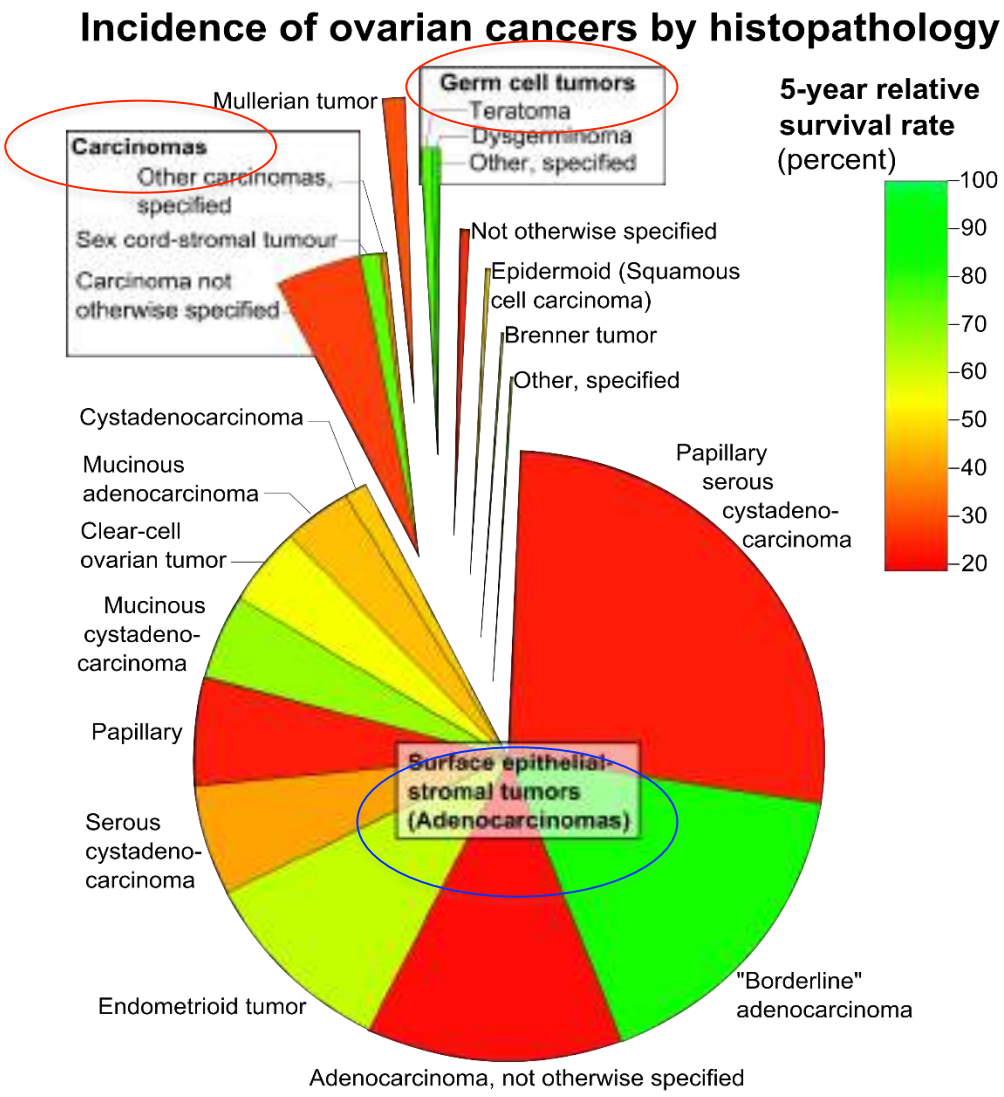




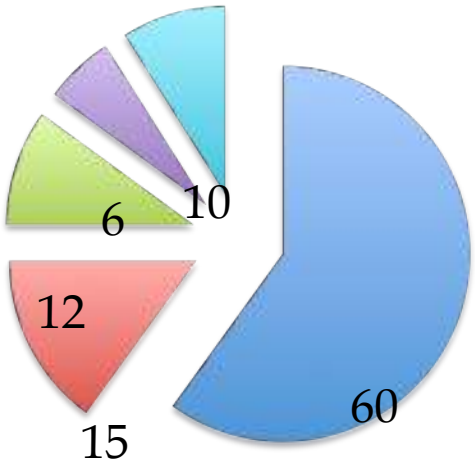
Ovarian cancer is a complex disease

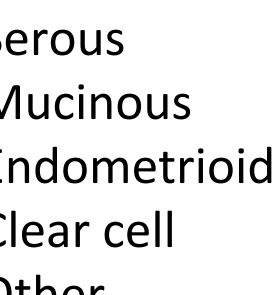


- Germ cell eg. dysgerminoma
- Sex cord – stromal/ carcinoma
- Epithelial (90%)

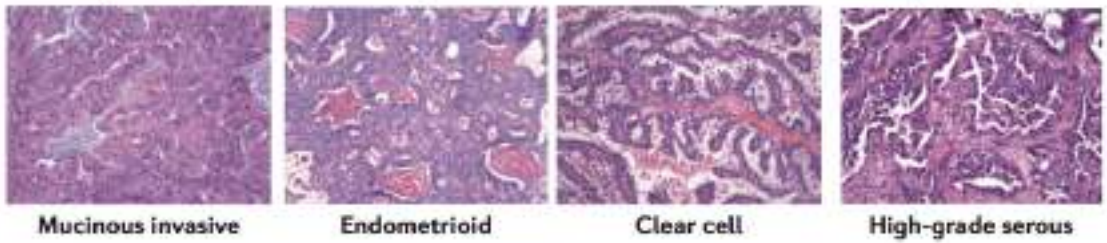
C. Kosary (2007) Cancers of the ovary (Chapter 16: *SEER Survival Monograph*)

Conventional classification of epithelial ovarian cancer



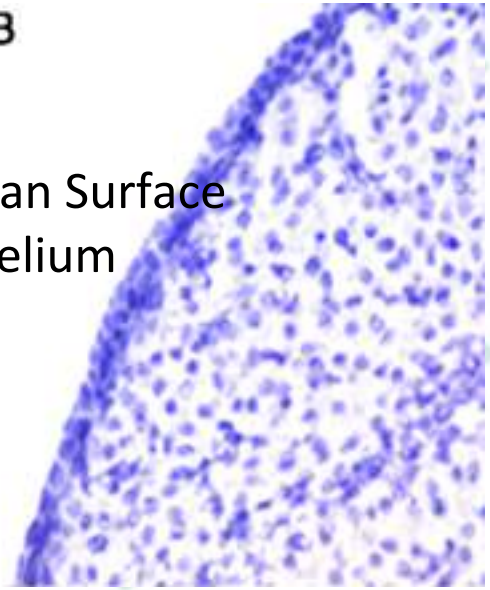


Serous
Mucinous
Endometrioid
Clear cell
Other



B

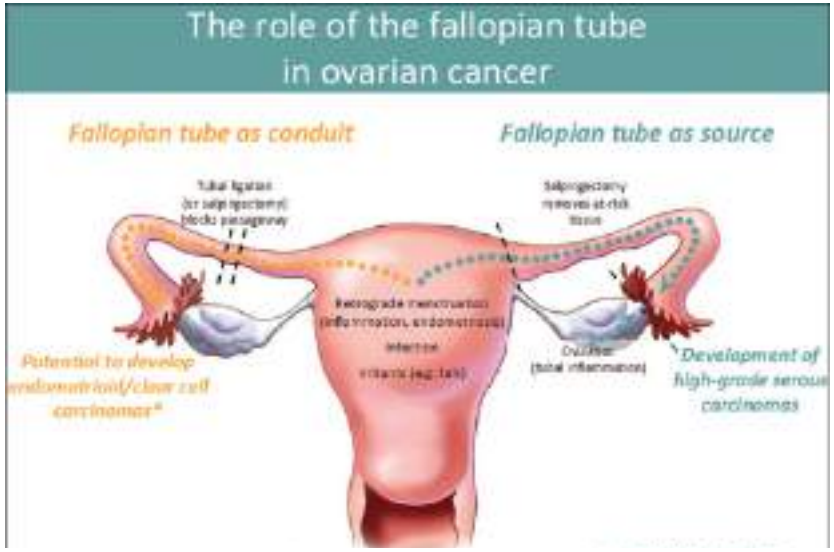
Ovarian Surface Epithelium

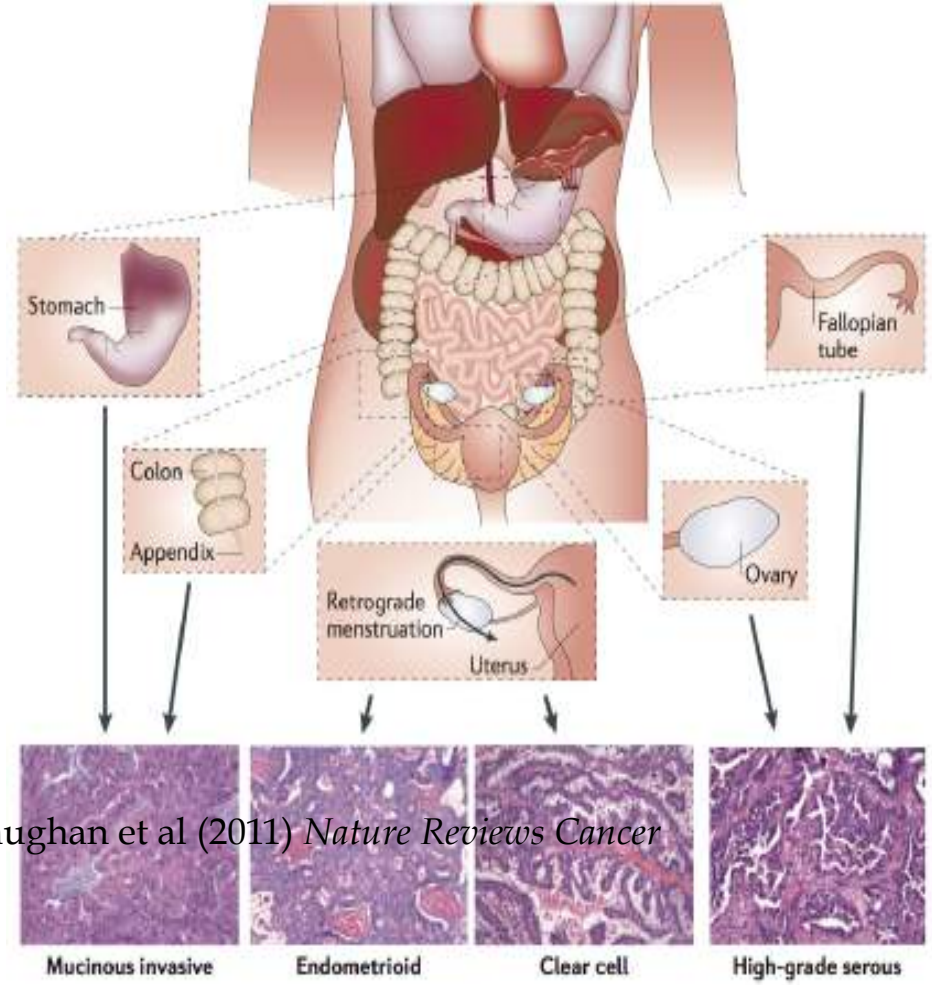


The most common types of ovarian cancer were thought to mostly arise from cells on the surface of the ovary

Ovarian cancer is a series of distinct diseases with different cells of origin

– mostly not from the ovary and all very different!



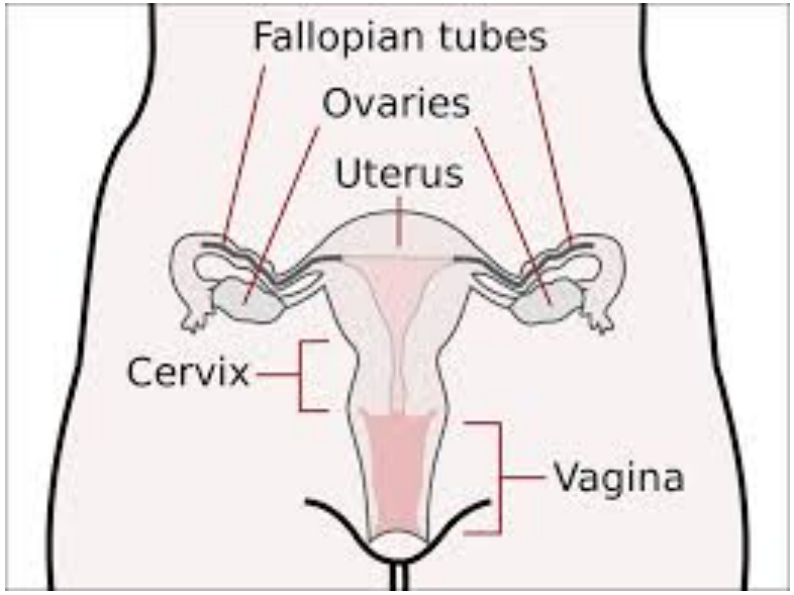


Vaughan et al (2011) *Nature Reviews Cancer*

Why the reclassification of ovarian cancer is important:

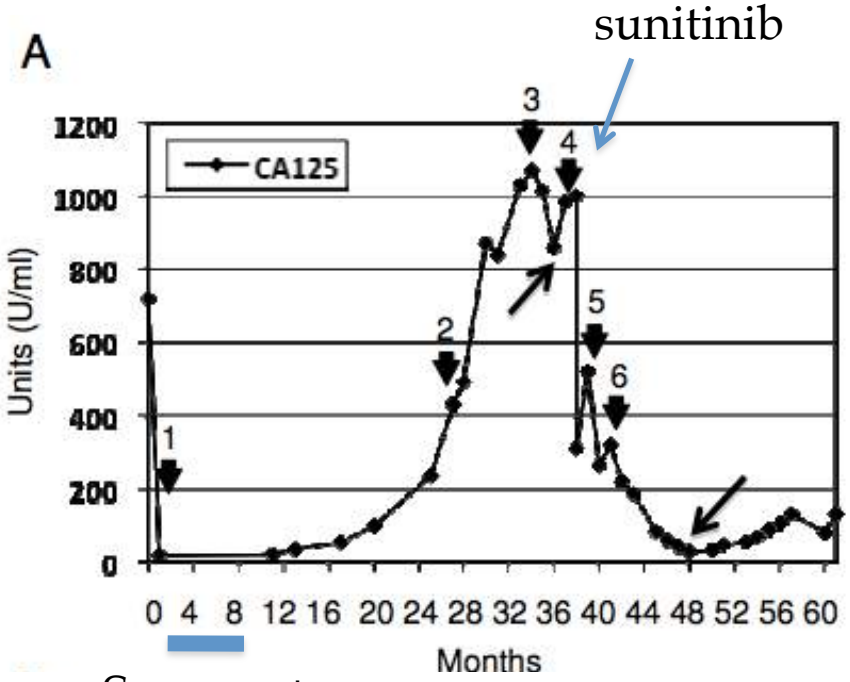
- Treatments need to be specific – not a one size fits all
- Genetic risk tracks with specific types – helps decide who should be offered testing
- We can't figure out the biology if they are all mixed together
- Knowing where they come from influences prevention (eg. removal of fallopian tubes) and early detection strategies

Refocusing risk reducing surgery in women with BRCA1 or BRCA2 mutations



- Removal of ovaries and fallopian tubes together?
- Removal of fallopian tubes only as this is where cancers associated with BRCA mutations arise?
- Fallopian tubes first and ovaries later?

Ovarian clear cell cancer genetic make up resembles renal clear cell cancer!



Surgery +
Platinum - taxol

Sunitinib is used in renal cancer

Anglesio et al (2011) *Clinical Cancer Research*

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First, what exactly is a gene?

Our genome is made of DNA packaged into chromosomes

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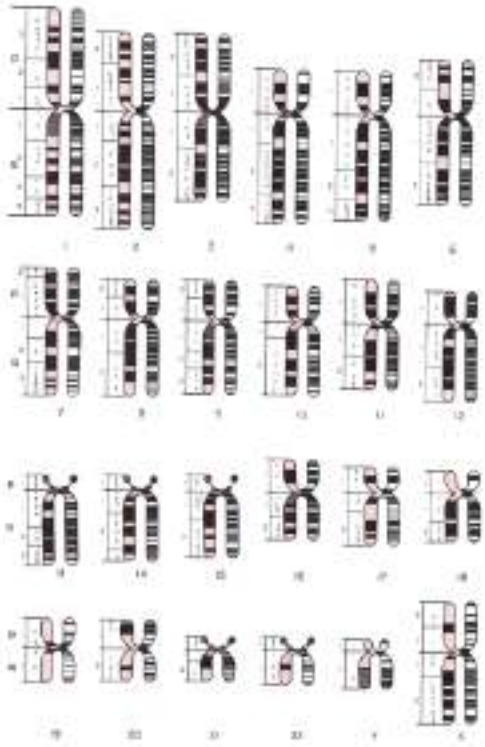
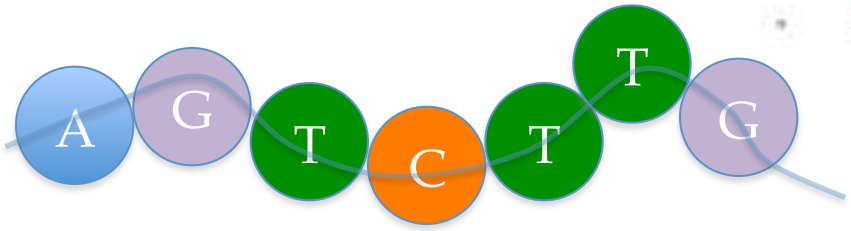


chromosomes



DNA

1st round — K3M, * K1C2, K5M, rep from * to last 3 sts, K1C2, K2M.

2nd round — As 1st round.

3rd round — K2M, * K3C2, K3M, rep from * to last 4 sts, K3C2, K1M.

4th round — * K1M, K2C2, K1C1, K2C2, rep from * to end.

5th round — K2C2, * K3C1, K3C2, rep from * to last 4 sts, K3C1, K1C2.

Rep 5th round 3 times.

9th round — * K1C2, K5C1, rep from * to end.

10th round — As 9th round.

11th round — Using C1, knit.

Size 14 only — 12th round — Using C1, * (K2 tog, K6) twice, K2 tog, K5, rep from * to end ... 240 sts.

Sizes 16, 18 and 20 only — 12th round — Using C1, * K2 tog, K (4-4-3), rep from * to end ... 240 sts.

All Sizes — 13th round — Using C1, knit.

14th round — * K1M, K5C1, rep from * to end.

15th round — K2M, * K3C1, K3M, rep from * to last 4 sts, K3C1, K1M.

16th round — K3M, * K1C1, K5M, rep from * to last 3 sts, K1C1, K2M.

17th round — Using M, knit.

18th round — Using C1, knit.

19th round — Using C1, * K2, K2 tog, rep from * to end ... 180 sts.

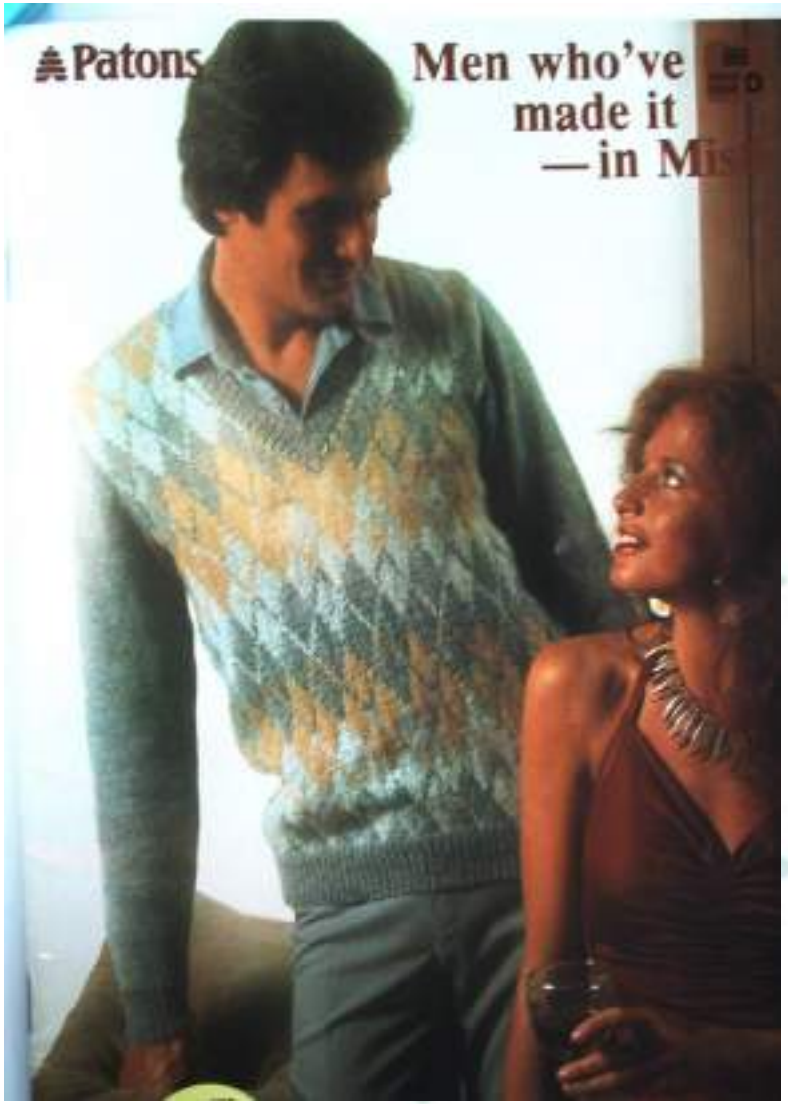
20th round — * K6C1, K4C2, rep from * to end.

21st round — K1C2, * K3C1, K7C2, rep from * to last 9 sts, K3C1, K6C2.

22nd round — K1C1, * K1C2, K1C1, K5C2, K3C1, rep from * to last 9 sts, K1C2, K1C1, K5C2, K2C1.

23rd round — K2C1, * K4C2, K6C1, rep from * to last 8 sts, K4C2, K4C1.

24th round — K1C1, * K4C2, K6C1, rep from * to last 9 sts, K4C2, K5C1.



1st round — K3M, * K1C2, K5M, rep from * to last 3 sts, K1C2, K2M.

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3rd round — K2M, * K3C2, K3M, rep from * to last 4 sts, K3C2, K1M.

4th round — * K1M, K2C2, K1C1, K2C2, rep from * to end.

5th round — K2C2, * K3C1, K3C2, rep from * to last 4 sts, K3C1, K1C2.

Rep 5th round 3 times.

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All Sizes — 13th round — Using C1, knit.

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15th round — K2M, * K3C1, K3M, rep from * to last 4 sts, K3C1, K1M.

16th round — K3M, * K1C1, K5M, rep from * to last 3 sts, K1C1, K2M.

17th round — Using M, knit.

18th round — Using C1, knit.

19th round — Using C1, * K2
sts.

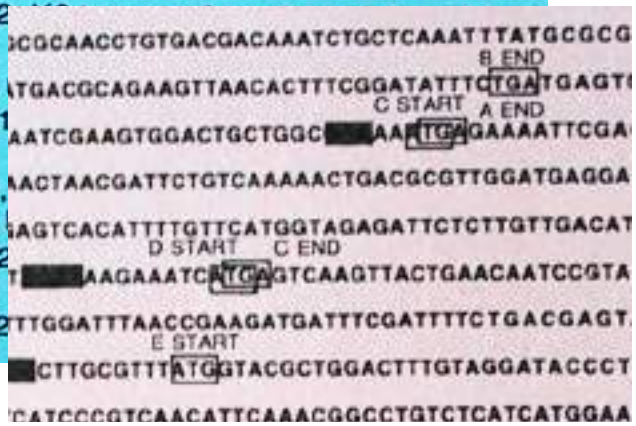
20th round — * K6C1, K4C2,

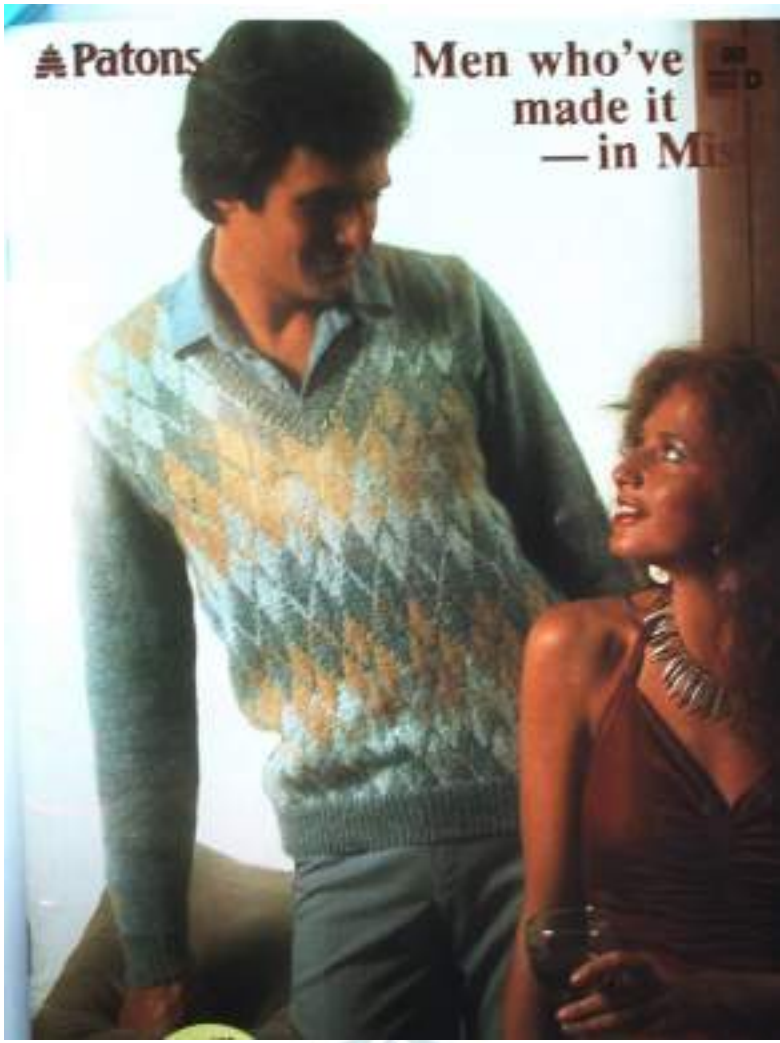
21st round — K1C2, * K3C1
K3C1, K6C2.

22nd round — K1C1, * K1C2,
last 9 sts, K1C2, K1C1, K5C2,

23rd round — K2C1, * K4C2
K4C2, K4C1.

24th round — K1C1, * K4C2
K4C2, K5C1.





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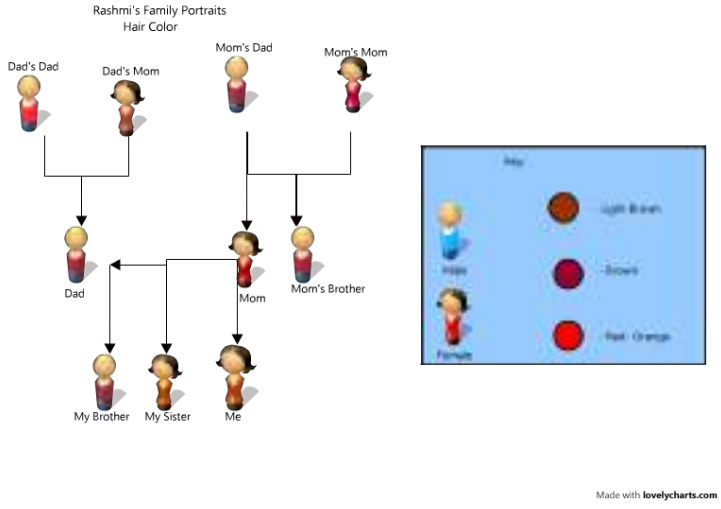
Ovarian cancer genetics



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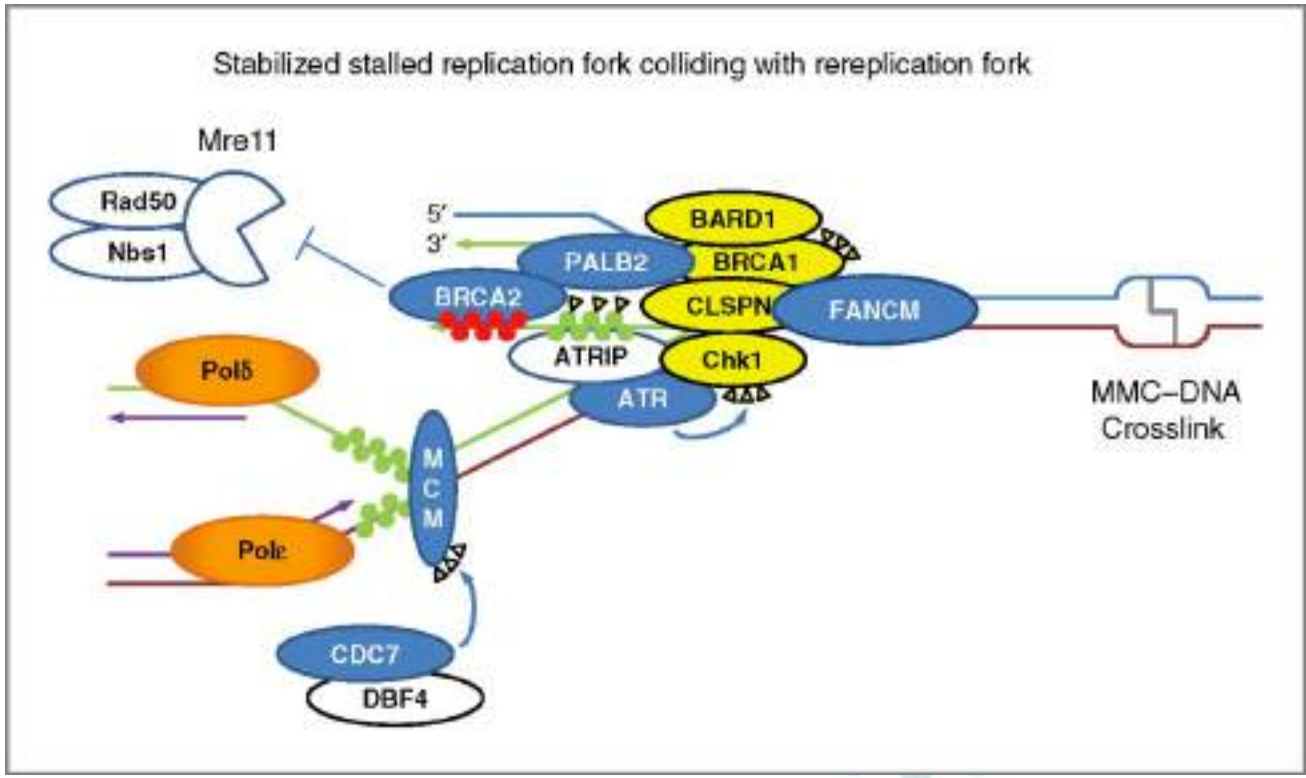
The BRCA1 and BRCA2 genes provide the blueprints for components of a nanomachine that very accurately repairs DNA



BRCA1 and BRCA2 mutations increase the risk of breast and ovarian cancer by 10-20X

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BRCA1/2 make proteins that are involved in DNA repair

Loss of one copy (mutation) increases the risk of breast and ovarian cancer (also some other cancers, eg. prostate cancer in men)

Mutation frequency was thought to be 5-10%

Testing was offered based on strong family history (and age of diagnosis)

Studies around the world, including a major Australian study changed that view

BRCA mutations in ovarian cancer

What was the real frequency of mutation?	17% of high grade serous cancers *Almost* only seen in these cancers
Should the genetic testing guidelines be changed?	Yes. Almost half of the carriers didn't' have a family history – so would be missed. Guidelines now changed
Did carrying a mutation influence treatment?	Yes. Better response to treatment and better survival. Persist with platinum.
Is it useful to know?	Yes. Risk of ovarian cancer can be reduced by 80-90%

Alsop et al (2012) *Journal of Clinical Oncology*

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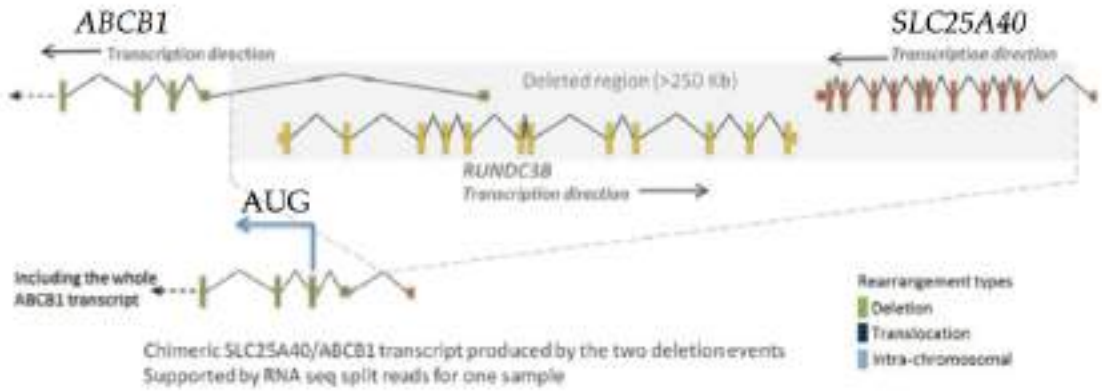
ARTICLE *Nature* May 2015

doi:10.1038/nature14410

Whole-genome characterization of chemoresistant ovarian cancer

Ann-Marie Patch[1,2]*, Elizabeth L. Christie[3]*, Dariush Etemadmoghadam[1,4,5]*, Dale W. Garsed[1]*, Joshy George[6], Sian Fereday[3], Katia Nones[1,7], Prue Cowin[3], Kathryn Alsop[1], Peter J. Bailey[1,7], Karin S. Kassahn[1,8], Felicity Newell[1], Michael C. J. Quinn[1,7], Stephen Kazakoff[1,2], Kelly Quek[1], Charlotte Wilhelm-Benartzi[9], Ed Curry[9], Huei San Leong[3], The Australian Ovarian Cancer Study Group†, Anne Hamilton[7,10,11], Linda Mileshkin[3,5], George Au-Yeung[3], Catherine Kennedy[12], Jillian Hung[12], Yoke-Eng Chiew[12], Paul Harnett[13], Michael Friedlander[3,5], Michael Quinn[11], Jan Pyman[11], Stephen Cordner[15], Patricia O'Brien[15], Jodie Ledittschke[15], Greg Young[15], Kate Strachan[15], Paul Waring[4], Walid Azar[3], Chris Mitchell[3], Nadia Traficante[3], Joy Hendley[3], Heather Thorne[3], Mark Shackleton[3,5], David K. Miller[1], Gisela Mir Arnau[1], Richard W. Tothill[1,3], Timothy P. Holloway[3], Timothy Semple[3], Ivon Harliwong[1], Craig Nourse[3], Ehsan Nourbakhsh[1], Suzanne Manning[3], Senel Idrisoglu[1], Timothy J. C. Bruxner[1], Angelika N. Christ[1], Barsha Poudel[1], Oliver Holmes[1,2], Matthew Anderson[1], Conrad Leonard[1,2], Andrew Lonie[16], Nathan Hall[17], Scott Wood[1,2], Darrin F. Taylor[1], Qinying Xu[1,2], J. Lynn Fink[1], Nick Waddell[1], Ronny Drapkin[18], Euan Stronach[9], Hani Gabra[9], Robert Brown[9], Andrea Jewell[19], Shivashankar H. Nagaraj[1], Emma Markham[1], Peter J. Wilson[1], Jason Ellul[3], Orla McNally[12], Maria A. Doyle[3], Ravikiran Vedururu[3], Collin Stewart[20], Ernst Lengyel[19], John V. Pearson[1,2], Nicola Waddell[1,2], Anna deFazio[12,§], Sean M. Grimmond[1,7,§] & David D. L. Bowtell[3,4,5,9,21,§]

Patients with high-grade serous ovarian cancer (HGSC) have experienced little improvement in overall survival, and standard treatment has not advanced beyond platinum-based combination chemotherapy, during the past 30 years. To understand the drivers of clinical phenotypes better, here we use whole-genome sequencing of tumour and germline DNA samples from 92 patients with primary refractory, resistant, sensitive and matched acquired resistant disease. We show that gene breakage commonly inactivates the tumour suppressors *RB1*, *NF1*, *RAD51B* and *PTEN* in HGSC, and contributes to acquired chemotherapy resistance. *CCNE1* amplification was common in primary resistant and refractory disease. We observed several molecular events associated with acquired resistance, including multiple independent reversions of germline *BRCA1* or *BRCA2* mutations in individual patients, loss of *BRCA1* promoter methylation, an alteration in molecular subtype, and recurrent promoter fusion associated with overexpression of the drug efflux pump MDR1.



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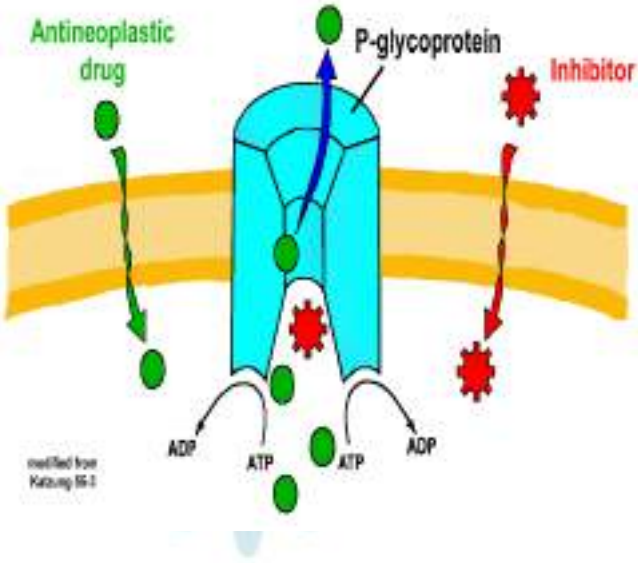
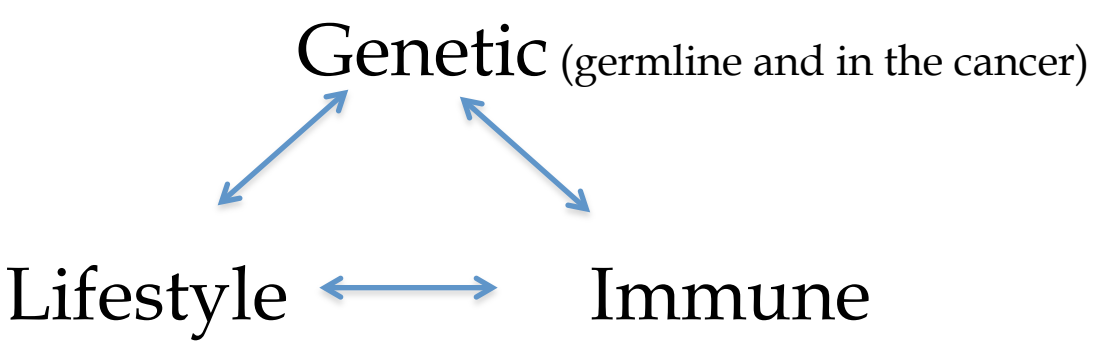
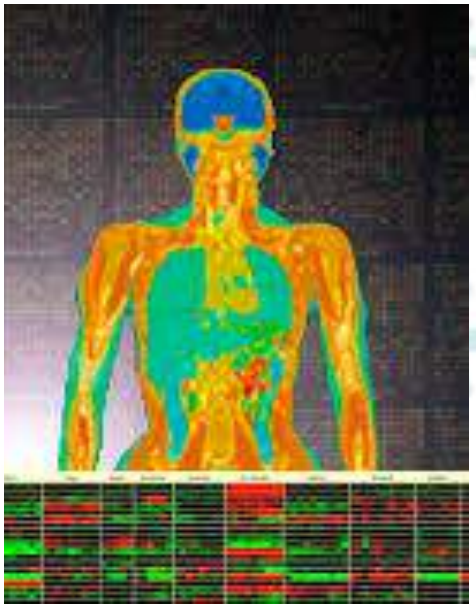
95 trillion bits of data



Understanding exceptional response

- International consortium (US, Canada, UK, Australia, Scandinavian countries)
- Australia leads the genome sequencing analysis
- Women with advanced high grade serous ovarian cancer who survive >10 years
- Recently funded by US Department of Defense





Summary

We have a much better idea of how the different types sort out – specific therapies, not one size fits all

Genetics is clearer – change the testing guidelines

Complete blueprint of all the mutations in common (and rare) forms – know what we are dealing with and can see new targets

Recurrence and acquired resistance – critical we understand this