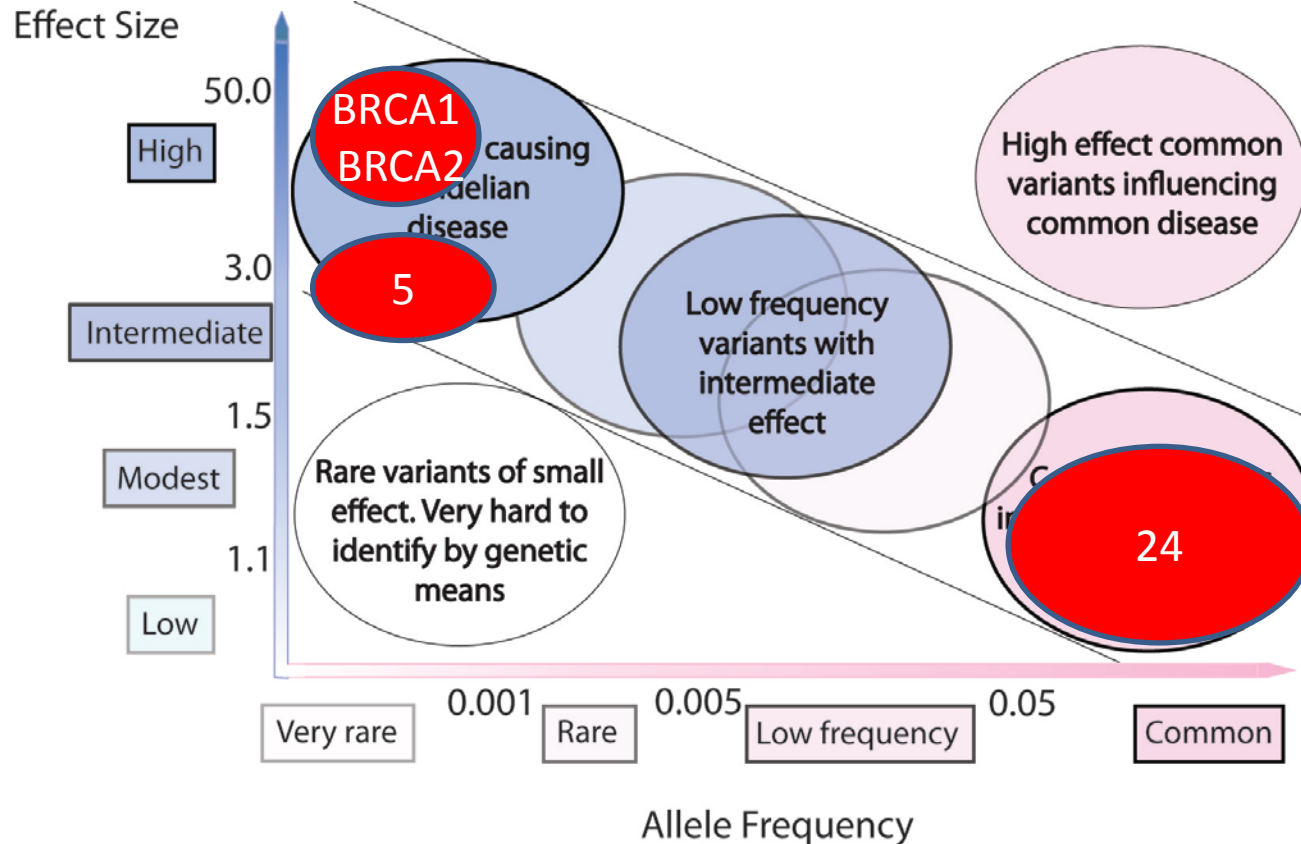# Clinical implementation of Cancer Susceptibility Genes

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Genetic predisposition to human disease

Manolio et al. 2009 Nature 461: 747-753

Familial case-control resequencing studies insights into VUS

- Full gene sequencing in >1000 familial cases and >1000 controls.
- Clear signal for truncating mutations.
- Multiple singleton rare missense mutations in *cases only*.
- Multiple singleton rare missense mutations in *controls only*.
- No significant difference in frequency, position, conservation, predicted functional impact between cases and controls.

Familial case-control resequencing studies insights into VUS

- Most missense variants in genes (that are inactivated to cause disease) are not disease causing.

- Most missense variants predicted *in silico* to be 'deleterious' are not disease-causing.

- It is very difficult to pick out the disease-causing missense variants.

- VUS should be considered and managed as 'innocent until proven guilty'.

Management of *BRCA1/2* carriers

Unaffected women

- At risk of breast cancer (50-80%)
- At risk of ovarian cancer (20-50%)
- Increased surveillance – annual MRI and mammograms
- Oophorectomy after completing family – greatly reduces ovarian and breast cancer risk
- Discuss bilateral mastectomy

Management of *BRCA1/2* carriers

 <u>Affected women</u>

- At risk of bilateral breast cancer

- At risk ovarian cancer

- Personalised treatment – e.g. PARP inhibitors

- <5% unselected breast cancer (higher in subgroups e.g. TNT breast cancer)

- >10% ovarian cancer

All women with breast or ovarian cancer should have access to BRCA testing.

Challenges to implementation

- Need cheap, quick testing – achievable.
- Need quick, simple report of results, that are readily understandable by non-genetic experts.
- Need simple triage into clinical actions.

Classification of *BRCA* variants

Class	Description Probability of being Pathogenic
5	Definitely Pathogenic >0.99
4	Likely Pathogenic 0.95–0.99
3	Uncertain 0.05–0.949
2	Likely Not Pathogenic or of Little Clinical Significance 0.001–0.049
1	Not Pathogenic or of No Clinical Significance <0.001

Problems:
Fairly arbitrary bins based on various assumptions.
Laborious and for many variants no data available to classify.
5 variant classes but only two clinical management categories.
Many variants in classes 2,3,4 managed as pathogenic.

Many hundreds of women are being recommended interventions, including preventative surgery, because they carry genetic variants which available evidence and paradigms indicate do not appreciably increase risk of cancer.

Clinical management based approach

Variant category

1 – benign
2 – not assignable
3 – possibly assignable
4 – pathogenic

Management category

Negative
(screen according to FH)

Positive

Default category for every variant is 2.
Variants have to be actively moved into another group.
Targeted research for class 3 variants

Transferable/scalable model?

- Key is to define the clinical management categories and to ensure that focus of variant evaluation is to triage to these.

- Scalable – as focus on attributing pathogenicity rather than evaluation of all variants.

- Monitoring of Class 3 variants required to ensure classification is iterative and uptodate.

- Urgent need for better *in silico* pathogenicity prediction. Without this most singleton missense variants will remain unassignable (Class 2).

RAD51C – a cautionary tale

- Nature Genetics 2010 – published as a high penetrance breast-ovarian gene comparable to *BRCA1/2*.

- OMIM entry

#613399 BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 3; BROVCA3

- BUT truncating mutations only in breast *and* ovarian families, NOT in 620 breast only families.

- Later missense mutations proposed to cause breast cancer – few controls studied.

RAD51C is not a high risk breast cancer gene

- Large case-control resequencing study.
- Ovarian cancer risk 5.88 (95%CI: 2.91-11.88; P=7.65x10^{-7})
- Breast cancer risk RR 0.91 (95%CI: 0.45-1.86; P=0.8)
- If gene causes phenotype A (ov ca) and you look for association with phenotype B (bc) *only* in relatives of phenotype A, will see an apparent association.
- 18-24 months after first gene report cancer risks clarified.
- If WGS in EMR was already routine, potential harm could have been considerable.

What do we need?

- Large-scale gene-specific population data
  - Clarify population specific polymorphisms.
  - Better information about the spectrum of pathogenic and non-pathogenic variants.
- Better predictive *in silico* methods.
- Standards for deciding if gene/variants are definitely pathogenic, particularly for newly discovered genes.