

Breast Cancer Genetics and Clinical Trials

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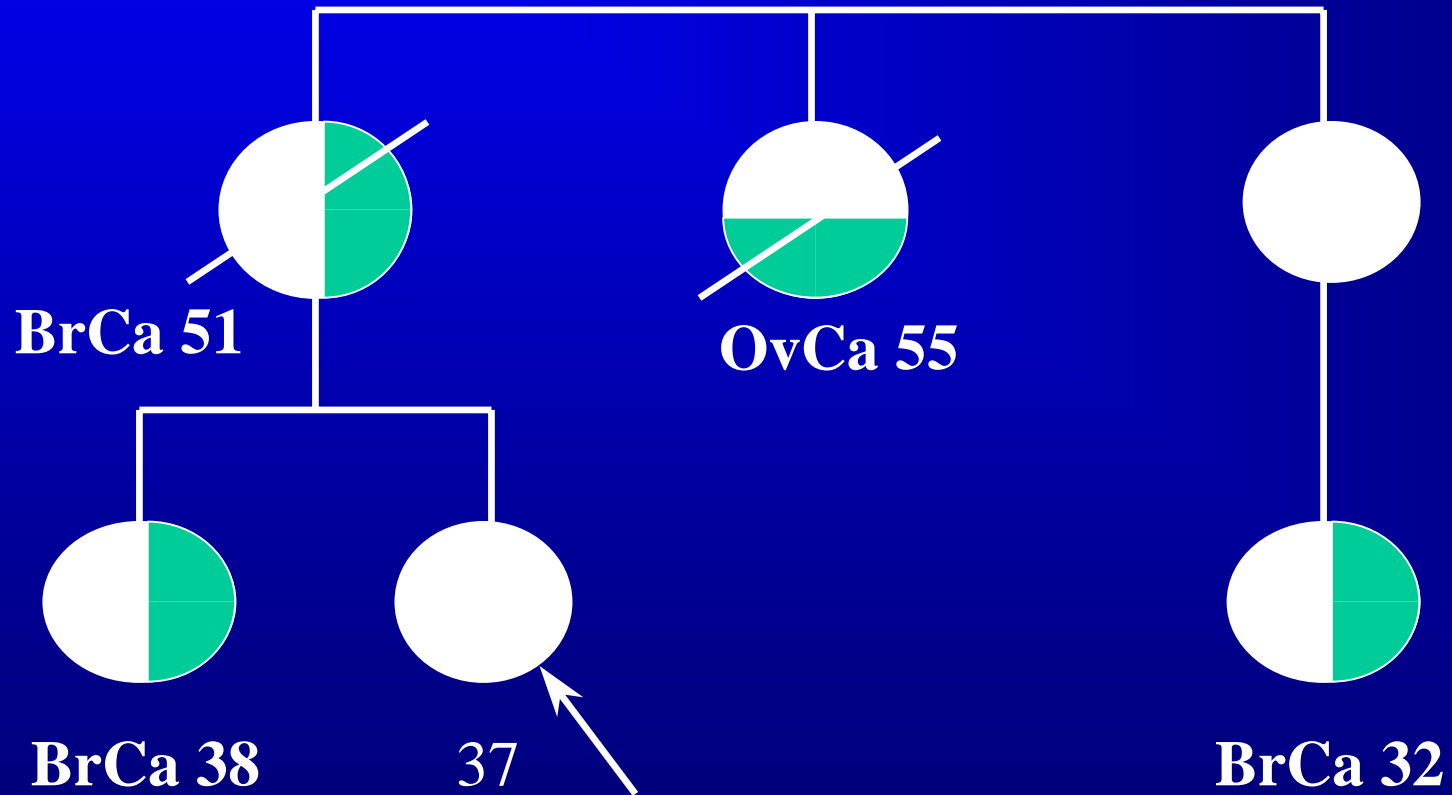
Inherited genetic variation and treatment outcome

Clinical Pharmaco-genetics

Summary

- Current practice in BRCA testing
- Genetic Breast Cancer Trial
- Acquiring new knowledge from routinely collected clinical oncology data
- A national structure for investigating pharmaco-genetics

High Risk



Genetic Testing

A 2 step process:

**1. identify mutation in affected
family member**

then

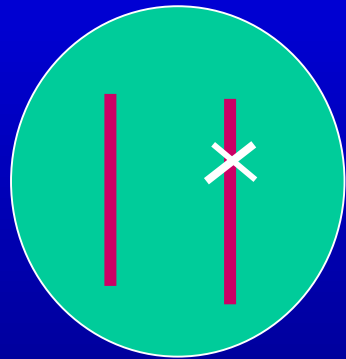
2. offer direct gene test



The Genetic Breast Cancer Trial

Breakthrough Breast Cancer
Cancer Research UK

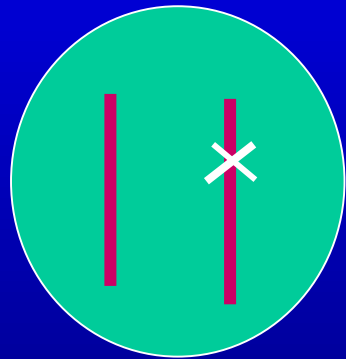
BRCA2 mutation carriers



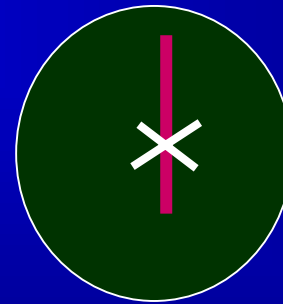
“Normal”

BRCA2 mutation carriers

Normal

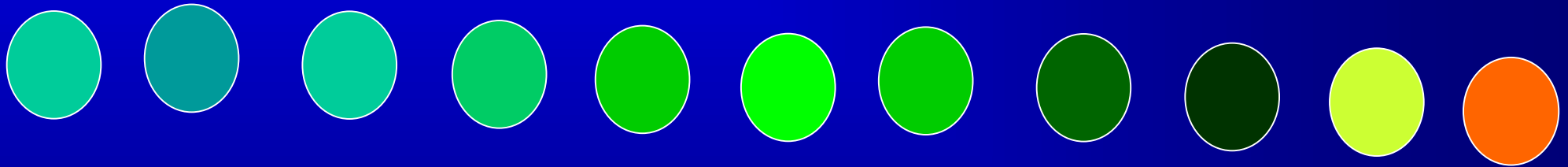


Tumour



Steps to becoming a cancer cell

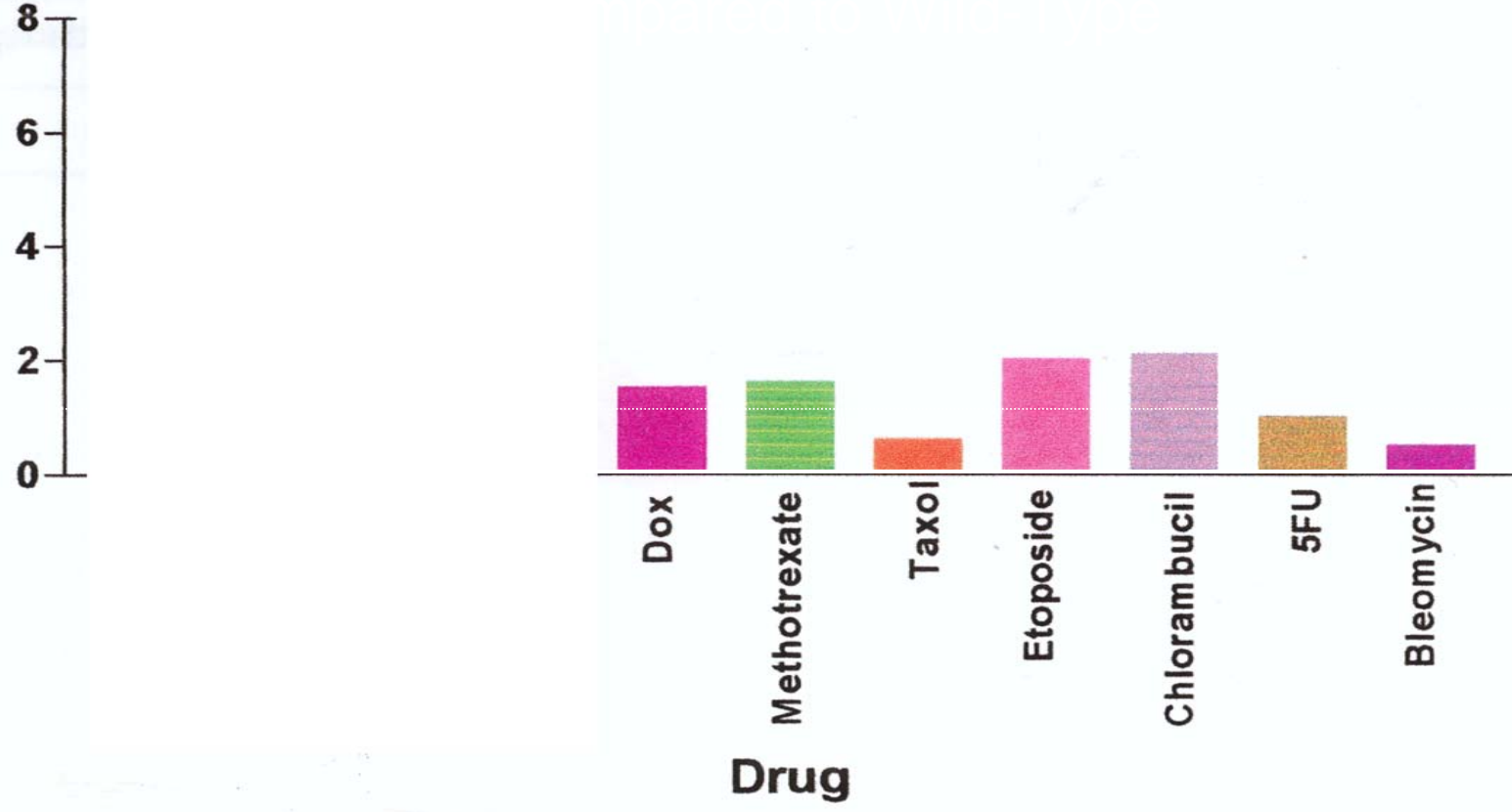
normal



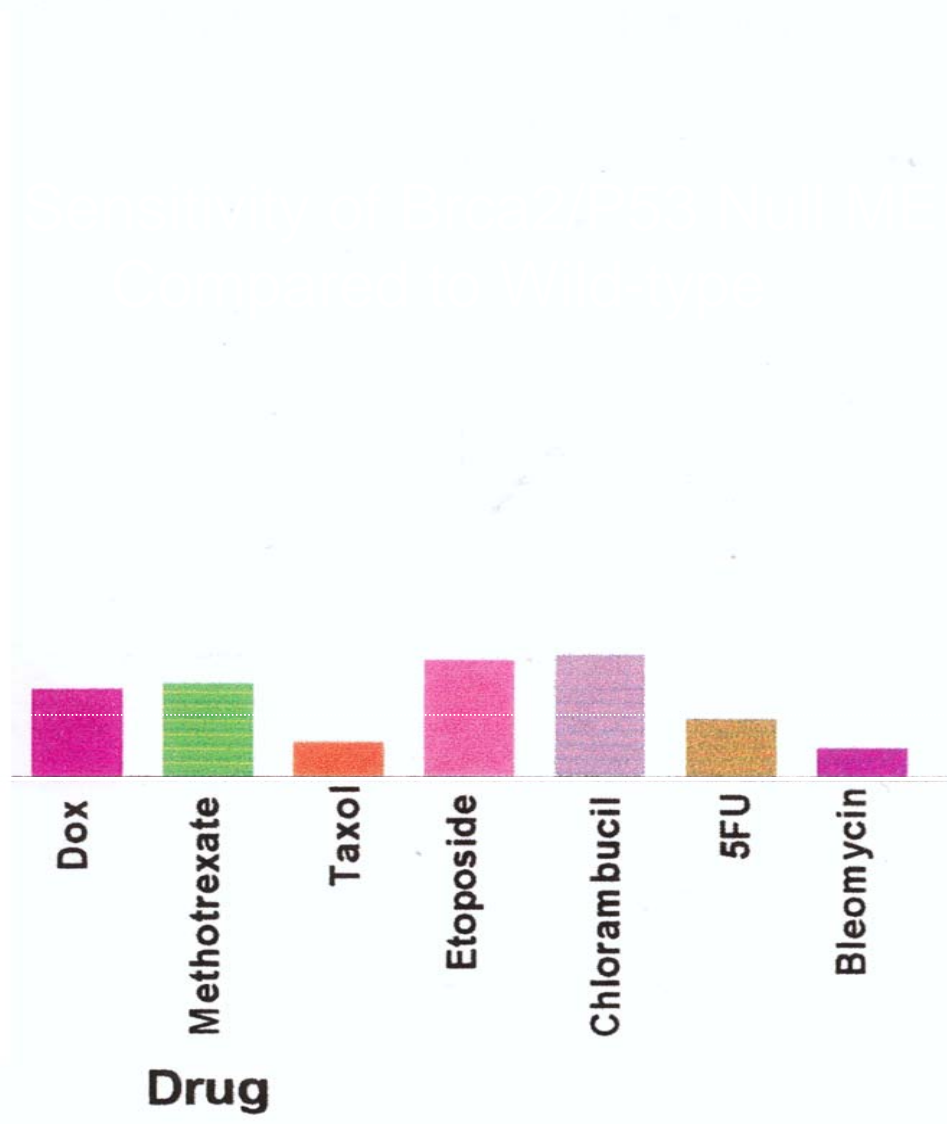
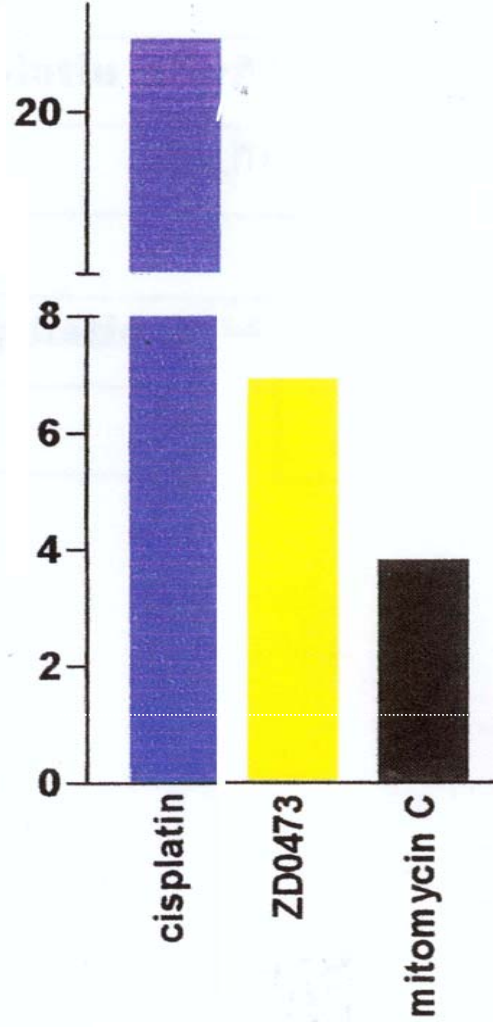
cancer

metastasis

Increased relative sensitivity
cells without Brca2



Increased relative sensitivity
cells without Brca2



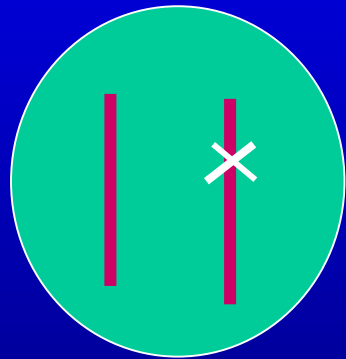
Alan Ashworth and the Breakthrough Breast Cancer Centre

- Protein encoded by BRCA2 in repair of DNA breaks
- Double strand DNA breaks repaired by two different mechanisms
- One path is error free but needs an intact BRCA2 pathway
- Second path works without BRCA2 but allows far more errors

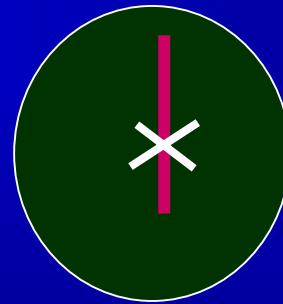
- The chemotherapy drug platinum causes double strand DNA breaks
- Cells without BRCA2 repair this damage by the error prone mechanisms
- These cells are therefore much more sensitive to platinum

BRCA2 mutation carriers

Normal



Tumour

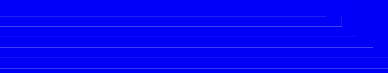


Clinical Hypothesis to test

- Are tumours in BRCA2 carriers more sensitive to platinum than other drugs?
- Is the normal tissue in BRCA2 carriers more sensitive to platinum than other drugs?

Optimal study design

- A randomised study in known BRCA carriers with breast cancer at relapse of a platinum versus a taxane
- Strong international support
- May be difficult to recruit enough volunteers
- First trial of chemotherapy based on inherited genetic make-up in the world



Deriving new knowledge from
routinely collected clinical data

The Clinisys clinical database

Originally designed as a best practice clinical treatment system

The database currently has data from

- 60 NHS trusts
- 2.4m patients
- Over 50 distinct disease categories
- 250 treatment protocols
- Patient data includes diagnostic information, histo-pathological information, routine laboratory measurements, tumour markers

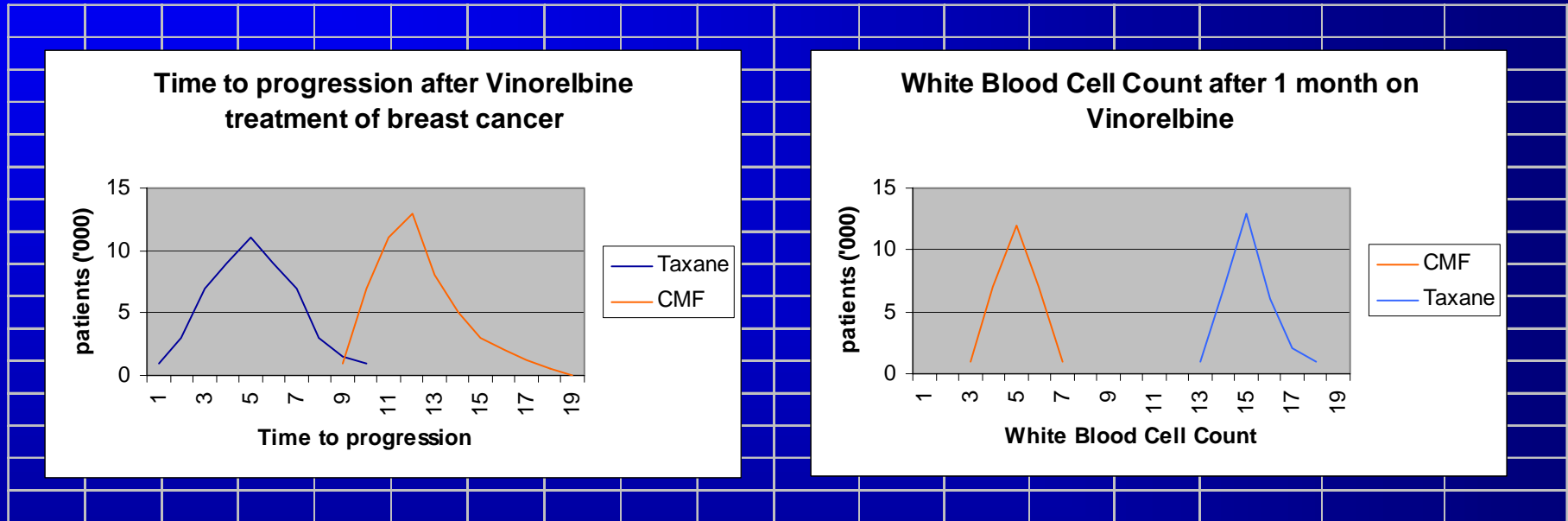
Objective is to refine inputs to the database to incorporate

- Improved outcomes measurements
- More specific questions relating to reason for changes in prescriptions/dosage

An example from metastatic breast cancer

- Vinorelbine (a new chemotherapy drug) is only given in metastatic breast cancer as second or third line
- Look at all the patients who have had vinorelbine
- Examine all the previous drug regimes they have had
- Compare the side-effect profile for the first two courses of vinorelbine (low platelets, low white blood count, severe vomiting) across patients who have had different preceding drug regimes; or even across patients who have had different numbers of drug regimes

Hypothetical example of differential toxicity



Vinorelbine is more effective as second line therapy after CMF then after Taxane



Toxicity of Vinorelbine is worse after CMF then after Taxane

Developing a national structure to pursue cancer pharmaco-genetic research

- Association between inherited genetic variation and clinical outcome – response to treatment
- Treatment response is the sum of toxicity profile and efficacy
- Toxicity profile is the response of normal cells
- Efficacy is the response of the tumour cells

Pharmaco-genetics in an adjuvant breast trial

- TACT 2 is a trial of accelerated chemotherapy in the adjuvant treatment of breast cancer
- We have secured funding to collect a single blood sample for analysis of constitutional DNA from all 4,000 patients
- Patient information sheet and consent form has been approved by MREC
- Awaiting some minor modifications relating to information on other trials

London Genetics

- A collaboration between several London medical schools and academic institutes
- Start up funding from the Department of Trade and Industry and the London Development Agency of £2 million
- To offer genetic services within clinical trial activity in a commercial environment
- Once established will align itself with national initiatives such as the National Cancer Tissue Resource
- Will start with oncology and then move into other disease areas, in parallel with the UK Clinical Research Collaboration, led by Leeds and UCL

Further developments

- Deputy director of the National Translational Cancer Research Network (NTRAC) has agreed to come and lead the crucial patient engagement work
- Aim to collect a blood sample from everyone in a NCRI sponsored clinical trial
- Improve Clinisys to record useful, accurate clinical outcome data
- Develop a pilot study in UCLH, collecting a blood sample from everyone with cancer treated in UCLH
- Roll this initiative into all the hospitals using Clinisys for data capture

Why should we do this work in the UK

- The NHS is gradually developing national standards for cancer care
- Many trusts are now willing to use the same system for recording of clinical data
- MRC funded large project on bringing IT into clinical trial activity
- The National Programme for IT in the NHS is the largest IT project the world has seen
- The NCRI Informatics Initiative will act as a catalyst for this type of activity

Conclusions

- Genetic Breast Cancer Trial
- The Clinisys system for collection of routine clinical data
- Examining inherited genetic variation and treatment response in clinical trials
- Pilot study within UCLH of cancer pharmaco-genetics in non-trial patients
- Build a national structure for pharmaco-genetic investigation in oncology, and then in other disease areas

