

Introduction to concepts and controversies

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SOME DEFINITIONS

- Personalised Medicine: An approach to both preventative care and drug therapy that is based on the individual's genetic & other relevant information
- Precision Medicine: Tailoring of medical treatment to the individual characteristics of each patient, usually involving patients being classified into subpopulations
- P4 Medicine: predictive, preventative, personalised and participatory medicine



TRADITIONAL VS PRECISION MEDICINE



Traditional approach is “one size“ fits all.
Blockbuster drug prescribed for “typical” patient

BUT not successful for everyone, as patients and
their environments are different

Precision medicine takes individual differences into account
“ The right medicine, at the right time at the right dose”



THE IDEA OF PRECISION MEDICINE IS NOT NEW

- 1902 Sir Archibald Garrod – inheritance of alkaptunoria
- 1907 Reuben Ottenberg first blood transfusion using blood compatibility testing
- 1956 United States Army Researchers discovered genetic basis of selective toxicity of primaquine, an anti malarial drug (glucose-6-phosphate dehydrogenase deficiency)
- 1977 Role of cytochrome p450 metabolising enzyme variation in overdose toxicity with desbrisoquine
- 2003 finish of human genome project – began real era of personalised medicine



WHERE DO WE STAND NOW?

- When human genome project started
 - 4 drugs with pharmacogenomic (PGx) information
- When human genome ended
 - 46 drugs with PGx information
- Now
 - 261 drugs with PGx information
 - 362 drug-biomarker pairs
- We move forward by using biomarkers
 - A biomarker is “a naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified.” [Oxford Dictionary]



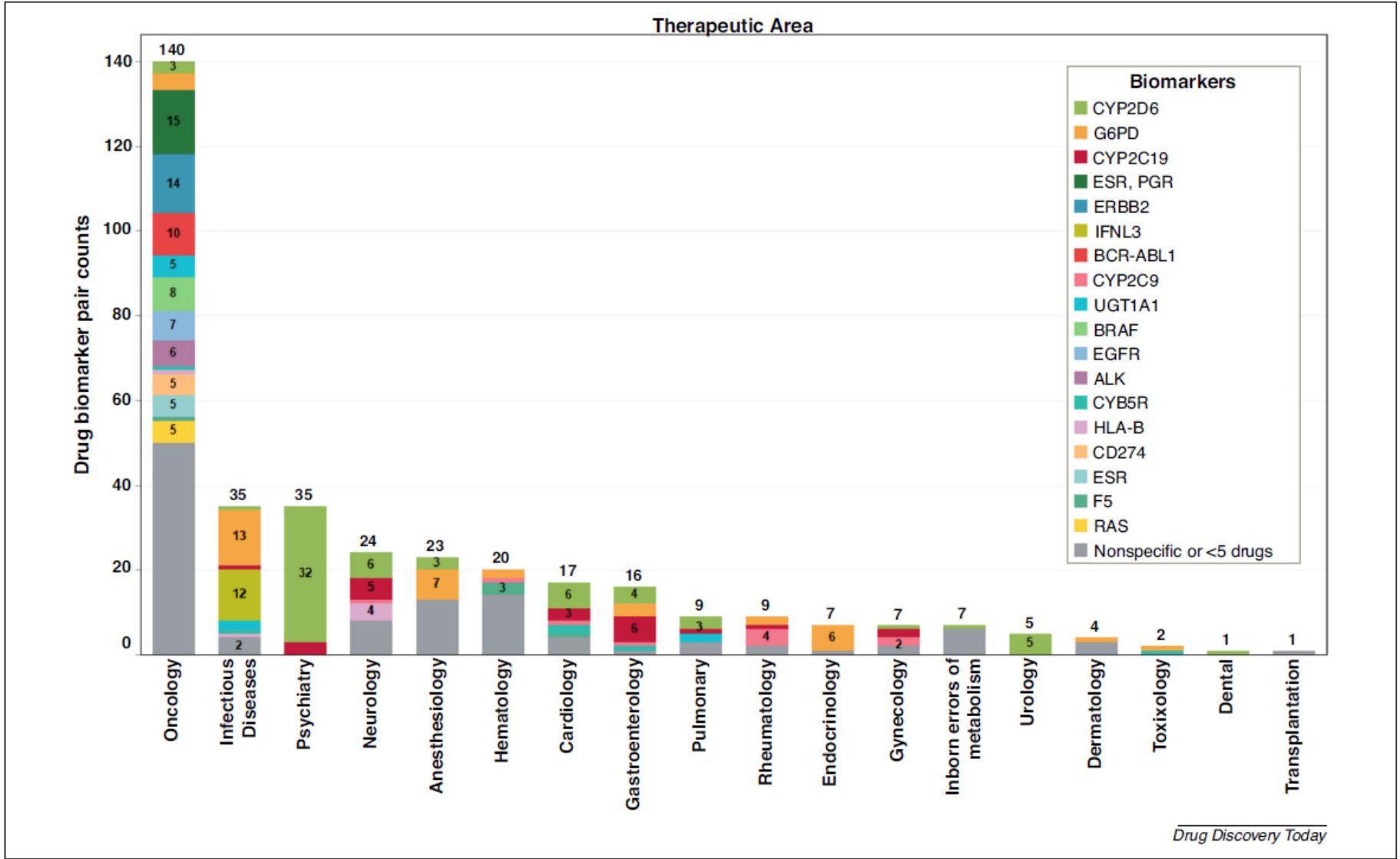


FIGURE 2

Therapeutic area (x axis) bar graph displays drug–biomarker pair counts (y axis) and 18 biomarkers (biomarkers ≥ 5 drugs shown) (color legend). The Oncology therapeutic class is highly diversified with multiple biomarkers.

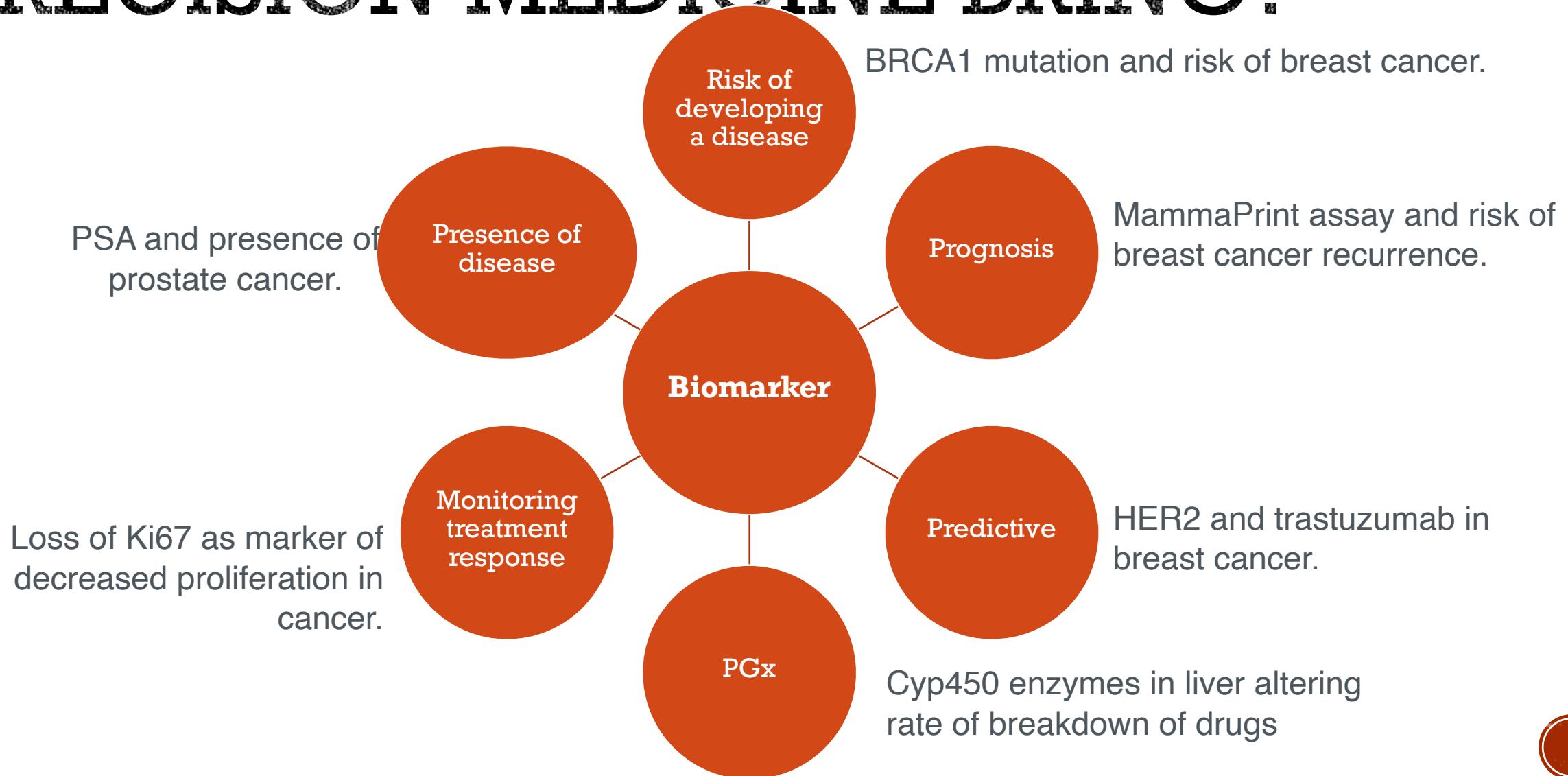


WHAT KIND CHANGES ARE WE LOOKING AT?

- Generally a change in function, expression, interaction, physiological measurement
 - specific cells, molecules, or genes, gene products, enzymes, metabolites or hormones
- Genomics
- Transcriptomics
- Proteomic
- Lipidomics
- Metabolomics
- Epigenomics



WHAT ADVANTAGE DOES PRECISION MEDICINE BRING?



- PSA (prostate-specific antigen) in prostate cancer
- PSA can be high for multiple reasons
 - Specificity is low: only 25-33% of men with high PSA have prostate cancer
- If a positive result received, may undergo biopsy
 - Stress
 - Costs
 - Risks (bleeding / infection)

PRESENCE OF A DISEASE

Diagnosis

- Helps identify person at risk of developing disease

EXAMPLE

- Breast and ovarian cancers
 - BRAC1 or BRAC2 gene
- +ve for mutation(s): 85% lifetime chance of breast cancer; 60% lifetime chance of ovarian cancer
- -ve for mutation(s): 13% lifetime chance of breast cancer; 0.7% lifetime chance of ovarian cancer

RISK OF DEVELOPING DISEASE

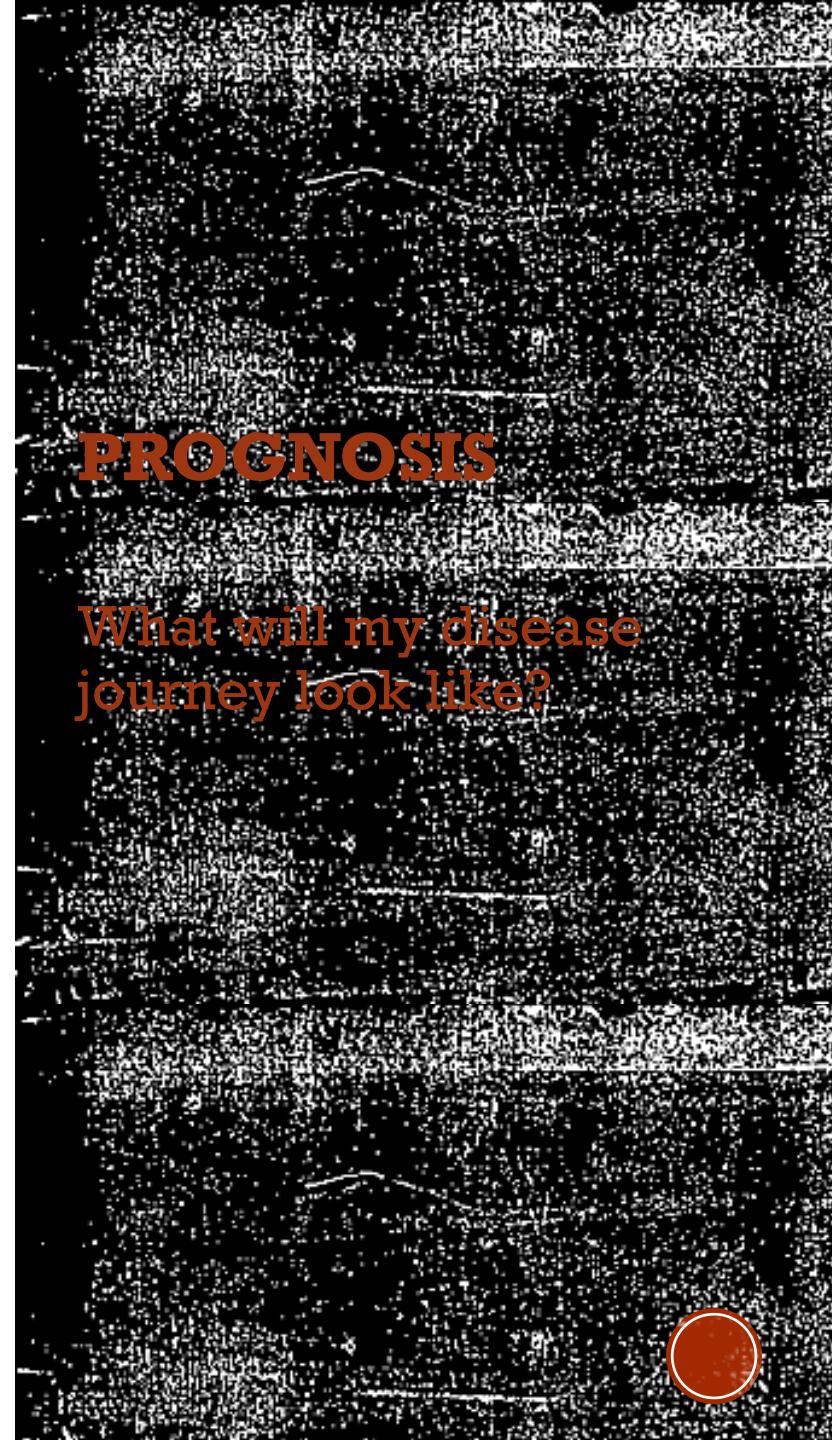
Predict susceptibility (risk) of developing disease

What is the likelihood of me developing this disease?



- **Mammaprint**

- are offered to help determine the risk of recurrence and to aid in the treatment decision making process.
- Utilise a number of biomarkers to help
- 70-gene risk of recurrence signature (70-GS, MammaPrint)
- 80-gene molecular subtype signature (80-GS, BluePrint) in early stage breast cancer patients.



PROGNOSIS

What will my disease journey look like?

- 25-30% patients with breast cancer are HER2 (human epidermal growth factor) positive
- Overexpress cell surface receptor (HER2 receptor)
 - Leads to abnormal cell growth
- Trastuzumab (Herceptin®) developed – in combination with chemotherapy 52% reduction in re-occurrence of tumour compared to chemotherapy alone
- Selectivity and specificity of test very high
- Reproducibility & type of test can be an issue

PREDICTIVE

IS A TREATMENT APPROPRIATE?

Targeting Therapy
based on molecular
diagnosis

Drug-Biomarker pairing



- Liver metabolising enzyme mutations
 - (enzymes that breakdown drugs)
- Cytochrome p450 family of enzymes
 - Responsible for metabolising >90% of drugs
- Thousands of mutations of genes in this family
- Leads to
 - Slow metabolisers: drugs metabolised very slowly
 - Overdose toxicity can occur
 - Normal metabolisers
 - Fast metabolisers
- Ultra fast metabolisers: drugs eliminated very quickly
 - Drugs are not effective

PHARMACOGENOMICS: IS THE DRUG SAFE?

Improves dosing,
increasing efficacy &
reducing side effects

Decreases adverse effects
of drugs

EXAMPLE

- Clopidogrel (Plavix®)– prevents blood clotting
- Commonly used in people with stents implanted to keep arteries open
 - Increased risk of clot formation
 - Clopidogrel can be taken to prevent clot formation
- Metabolised by CYP 2C19 (one of the cytochrome P450 enzymes)
 - Converts inactive drug to active drug
 - Variations lead to less conversion to active state
 - 25-30% patients at 3fold higher risk of clotting after stent implantation
- Genetic testing to identify poor metabolisers allows alternative treatment to be prescribed



- Ki67 in cancer
- The expression of Ki67 is strongly associated with tumour cell proliferation and growth
- The nuclear protein Ki67 (pKi67) is an established indicator for the assessment of biopsies from patients with cancer.
- Clinically, pKi67 has been shown to correlate with metastasis and the clinical stage of tumours.

OR

- A reduction in Ki67 can be used as an indication that less cancer cells are present and therefore a treatment is working

MONITORING WHETHER A DISEASE IS RESPONDING



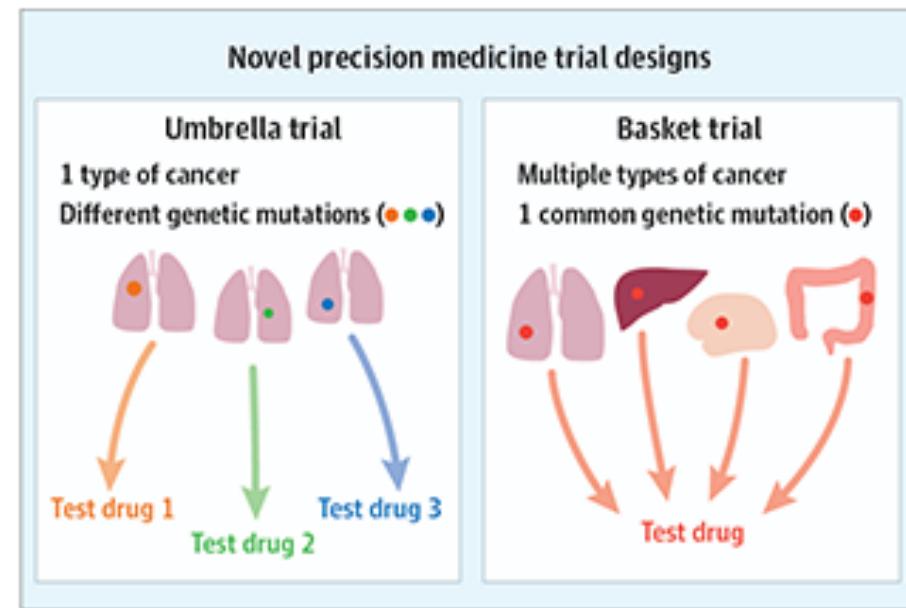
BENEFITS OF BIOMARKERS AND PRECISION MEDICINE

- Some allow option of changing lifestyle / environment to decrease chance of risk of developing disease
 - eg cardiac arrest or lung cancer
- Some allow decisions to be taken early (BRAC1 / 2)
- Some can aid drug development



REDUCES COST, ATTRITION RATE & TIME IN DRUG DEVELOPMENT

- Stratifying patients for clinical trials
 - Changing way clinical trials are run
- Maybe easier to pick up effect in same mutation group rather than mixed population
- Improves chance of positive outcome rather than negative outcome

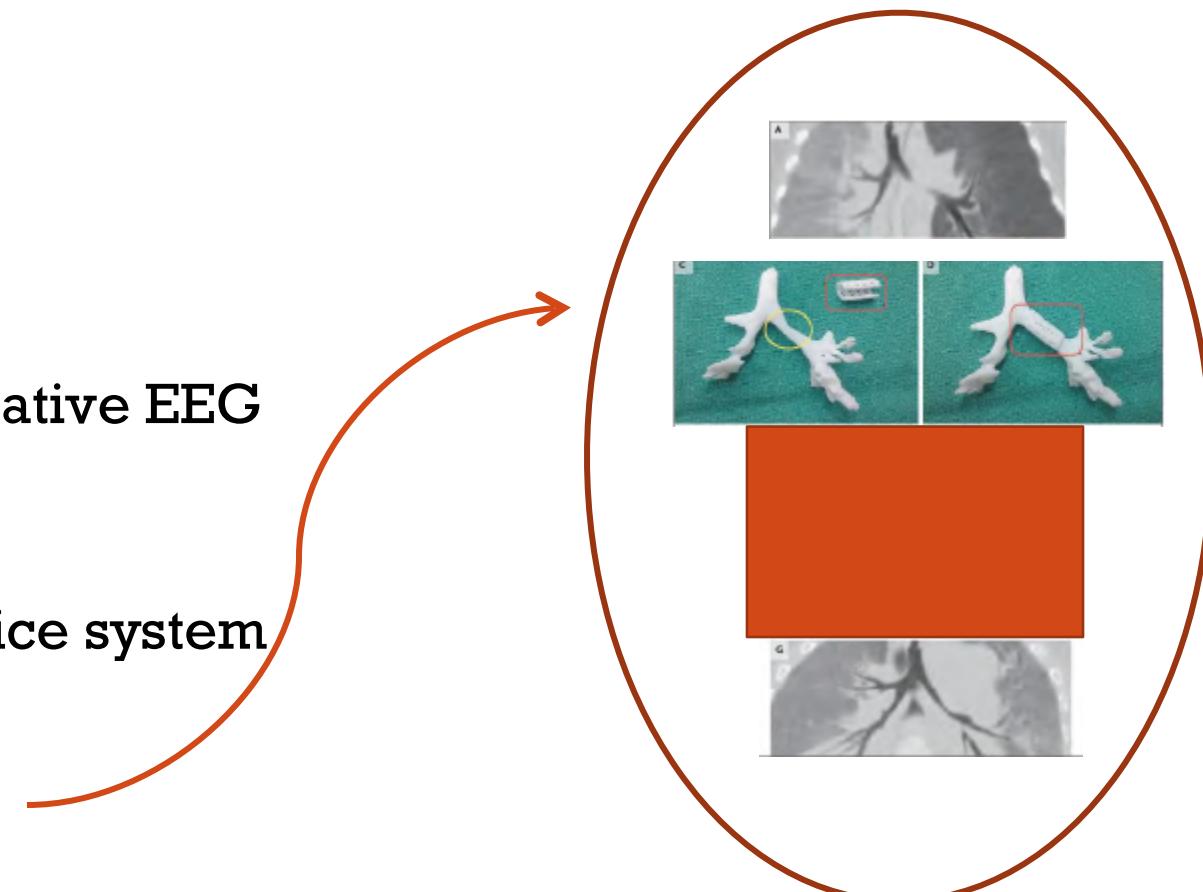


JAMA Oncology: doi:10.1001/jamaoncol.2016.5299



PRECISION MEDICINE IS NOT LIMITED TO GENES AND DRUGS....

- Can be devices too:
- Tinnitus masker
- Software-based quantitative EEG analysis
- Artificial pancreas device system
- Custom made splints



N Engl J Med 2013;
368:2043-2045.



CONTROVERCIES

- Ethics
- Multiple gene mutations / variations
- Statistics in genomics



ETHICS

- Once our genome has been sequenced
 - Who sees our data?
 - How will it be stored?
 - How will it be used?
 - Can it be used against us?
 - What legal protection do we have?
- What if the test is wrong?



MULTIPLE GENE MUTATIONS / VARIATIONS

- Gene mutations
 - Identify cancer causing gene
 - Have all mutations been identified?
 - A second mutation may render targeted therapy ineffective
 - Driver mutations & passenger mutations
 - Is driver mutation targeted by therapy or not?
- Gene variations
 - Work carried out by groups at The Karolinska Institute (Sweden)
 - Shown > 60000 variations in cytochrome P450 metabolising enzymes
 - 90% rare; 50% new findings (2015)
 - Each person carries >1000 gene variations that determine response to drug
 - Currently tests only cover a fraction of the relevant genetic variations
 - Therefore pharmacogenomics for drug dosing fairly ineffectual



STATISTICS IN 'OMICS

- These chip technologies for detecting 'omics
 - Cover thousands of genes
 - Or SNPs
 - Or proteins
 - Or enzymes / proteins / genes
- How do we cope with handling and assessing the data?
 - Are our statistical methods and patients sampling robust enough to interpret the magnitude of data?
- **Artificial Intelligence** could have the answer



DOES PRECISION MEDICINE WORK?

- Headlines include
 - “Precision medicine failing to deliver”
 - “Precision medicine fails for up to 93% of patients. Are its proponents selling 'false hope'?”
- Steve Jobs (Apple Chief Executive)
 - Paid \$100,000 to have his normal tissue and pancreatic tumour sequenced
 - Multiple attempts at targeted therapies
 - Dies within ~1 year of sequencing



A SUCCESS STORY....

- Dr Lukus Wartman
 - Cancer genome sequenced
 - Gene identified as being in “overdrive”
 - Targeted treatment given
 - Still in remission 15 years on
 - <https://www.ascopost.com/issues/november-10-2018/without-genomic-sequencing-i-would-not-be-alive-today/>



BENEFICIAL OR NOT? SOMETHING FOR YOU TO THINK ABOUT



“DNA-screening test 23andMe launches in UK after US ban”

“The Google-backed genotyping service can screen for common genetic diseases such as cystic fibrosis or sickle cell anaemia”

