



ST JOHN OF GOD PATHOLOGY

**Ethical and Legal Considerations in
Molecular Testing**

Dr Nik Zeps

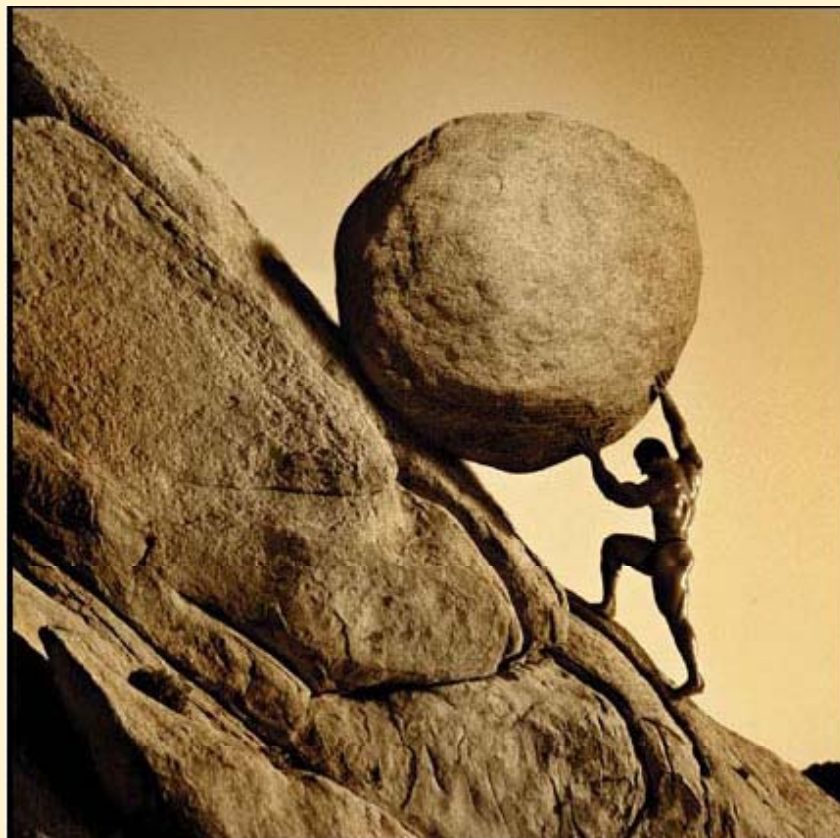
What is Ethics?

- Moral philosophy
 - Right and wrong
 - Good and bad
 - Justice and virtue

The Golden Rule

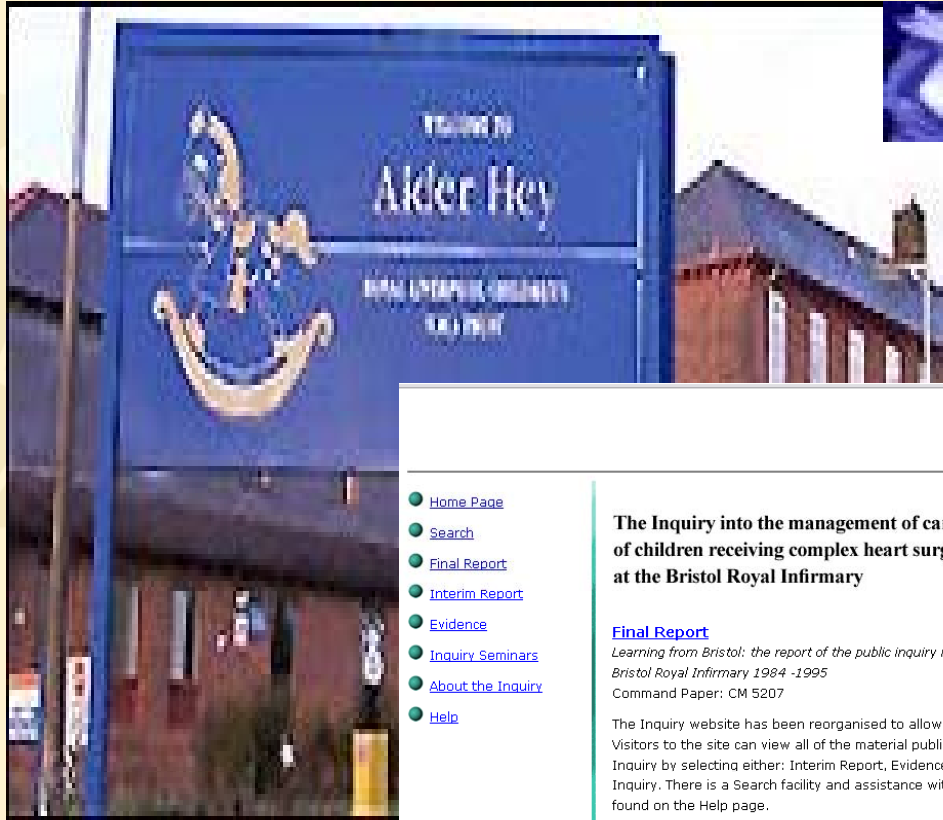
Avoid doing what you would blame others
for doing (Thales 624-546 BCE)

“getting” ethics



Ethical guidelines for pathology practice?

- There are none
- National Statement research only
- S95aa on privacy act
- NPAAC comment on consent
 - Phenotypic test vs hereditary
- Consent is magical bullet
 - Who does this?
 - Cost of roll out?
 - Peter Furness put it at \$10's millions for network of RNs



The Bristol
Royal Infirmary
Inquiry

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The Inquiry into the management of care of children receiving complex heart surgery at the Bristol Royal Infirmary

[Final Report](#)

Learning from Bristol: the report of the public inquiry into children's heart surgery at the Bristol Royal Infirmary 1984 -1995
Command Paper: CM 5207

The Inquiry website has been reorganised to allow easy access to the Final Report. Visitors to the site can view all of the material published throughout the course of the Inquiry by selecting either: Interim Report, Evidence, Inquiry Seminars or About the Inquiry. There is a Search facility and assistance with navigating the site can be found on the Help page.

The Welsh language version of the Summary and Recommendations is available [here](#).

Mae fersiwn Cymraeg o'r Crynodeb a'r Argymhellion ar gael [yma](#).

Published by the Bristol Royal Infirmary Inquiry, July 2001
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[BACK](#)[English](#)
[Swedish](#)

Press Release: The 2005 Nobel Prize in Physiology or Medicine

3 October 2005

The Nobel Assembly at Karolinska Institutet has today decided to award

The Nobel Prize in Physiology or Medicine for 2005

jointly to

Barry J. Marshall and **J. Robin Warren**

for their discovery of

"the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease"

Requirements for a *research tissue bank* to undertake this study?

- Human gastric mucosa
 - With and without gastritis
- EITHER surplus material left after routine diagnosis
- OR take extra biopsies specifically for research
- (No cost!!!)

Aspects of Marshall & Warren's study...

- Extra stains on 100 archival gastric biopsies
 - Was there any fear of risk to the patients?
- Investigators also had clinical responsibility
 - What is the effect on requirements for confidentiality?
- The study was unfunded
 - Therefore not peer reviewed or 'respectable'
- The study was highly speculative
 - So how many bureaucratic hoops would the researchers tolerate before giving up?

Waiver of Consent

- Section 2.3.6 of the NS
 - A) low risk
 - B) benefits outweigh harms
 - C) Impracticable to get consent
 - D) No reason why a person would say no
 - E) Privacy protected
 - F) Adequate plan to protect confidentiality
 - G) A plan to feedback results (or not)
 - H) Commercial outcomes will not cause disadvantage
 - I) Waiver is not unlawful

WA Colorectal
Research Group



Medical Research

I have read the Information Brochure entitled “WA Colorectal Research Group”, and Give my voluntary consent to the use of my biological specimens and health information for medical research as described therein.

Agree/Disagree (delete as appropriate)

Signed

Name (printed)_____

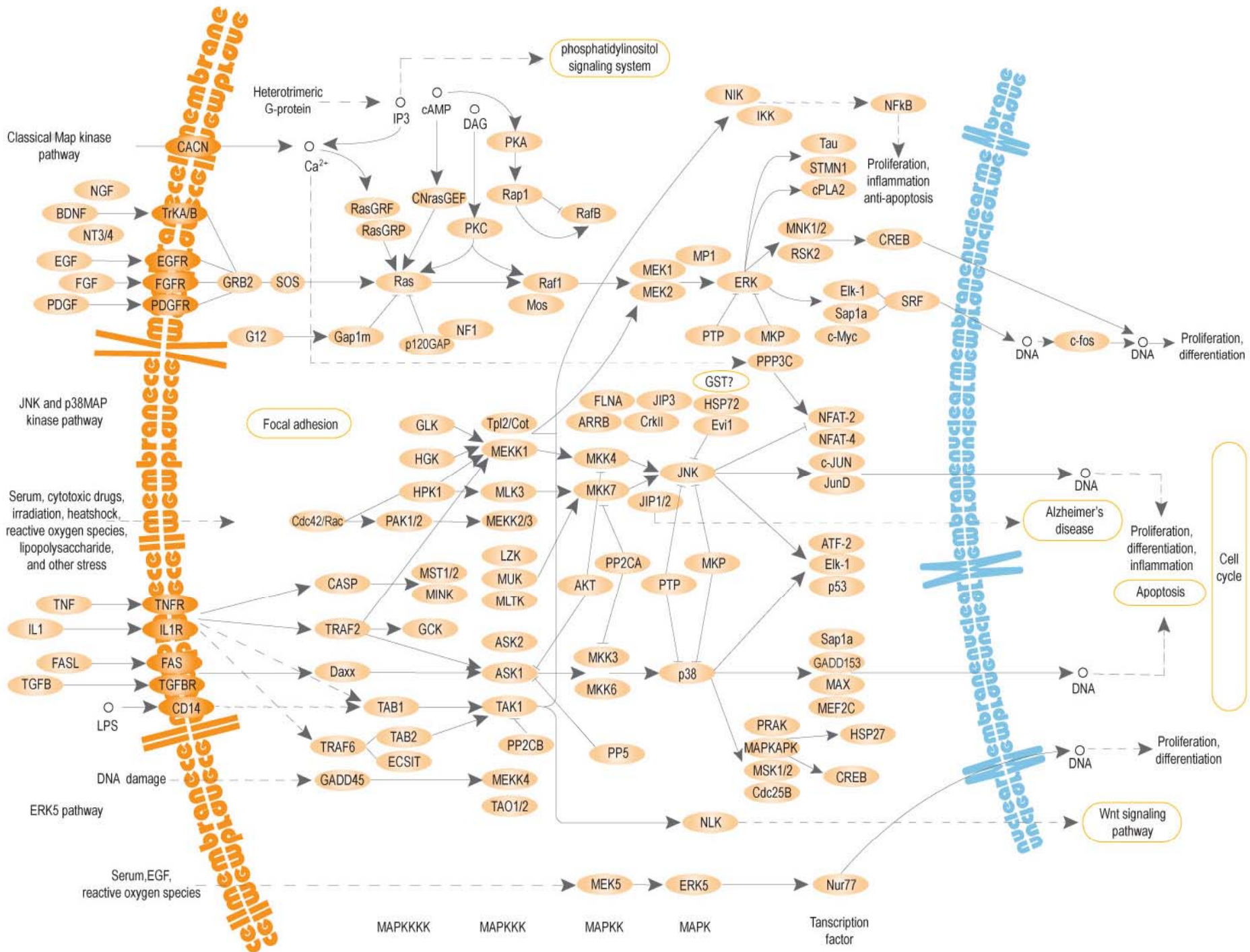
Date

Routine consent to procedure

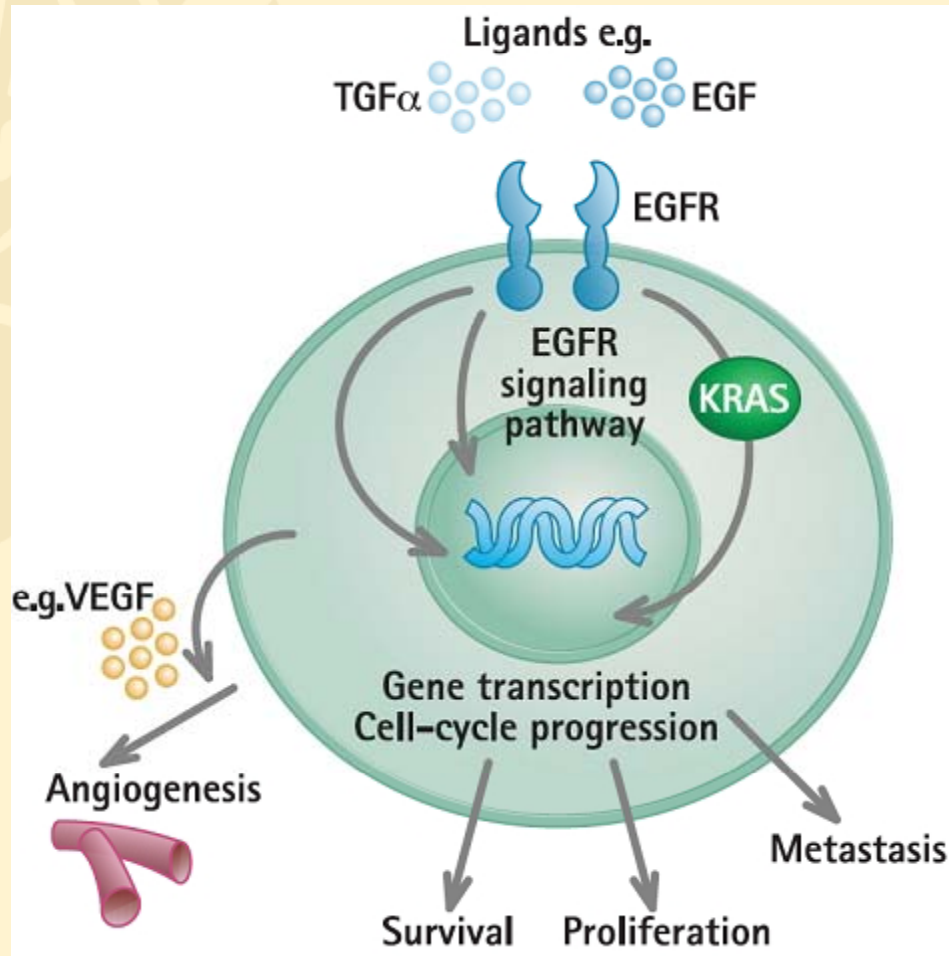
- That molecular diagnosis will occur
- That any left over samples will be used for research
- Our experience indicates
 - 99.99% approval
 - Cost effective

Genetic Information

- Is it Exceptional?
 - Different to any other information?
 - Predictive
 - Deterministic
 - Nature versus nurture
 - Genes versus environment
 - Redundancy



The EGFR pathway & KRAS



KRAS protein regulates downstream proteins in the EGFR signaling pathway associated with tumor survival, angiogenesis, proliferation and metastasis

wild-type KRAS: "normal", non-mutated

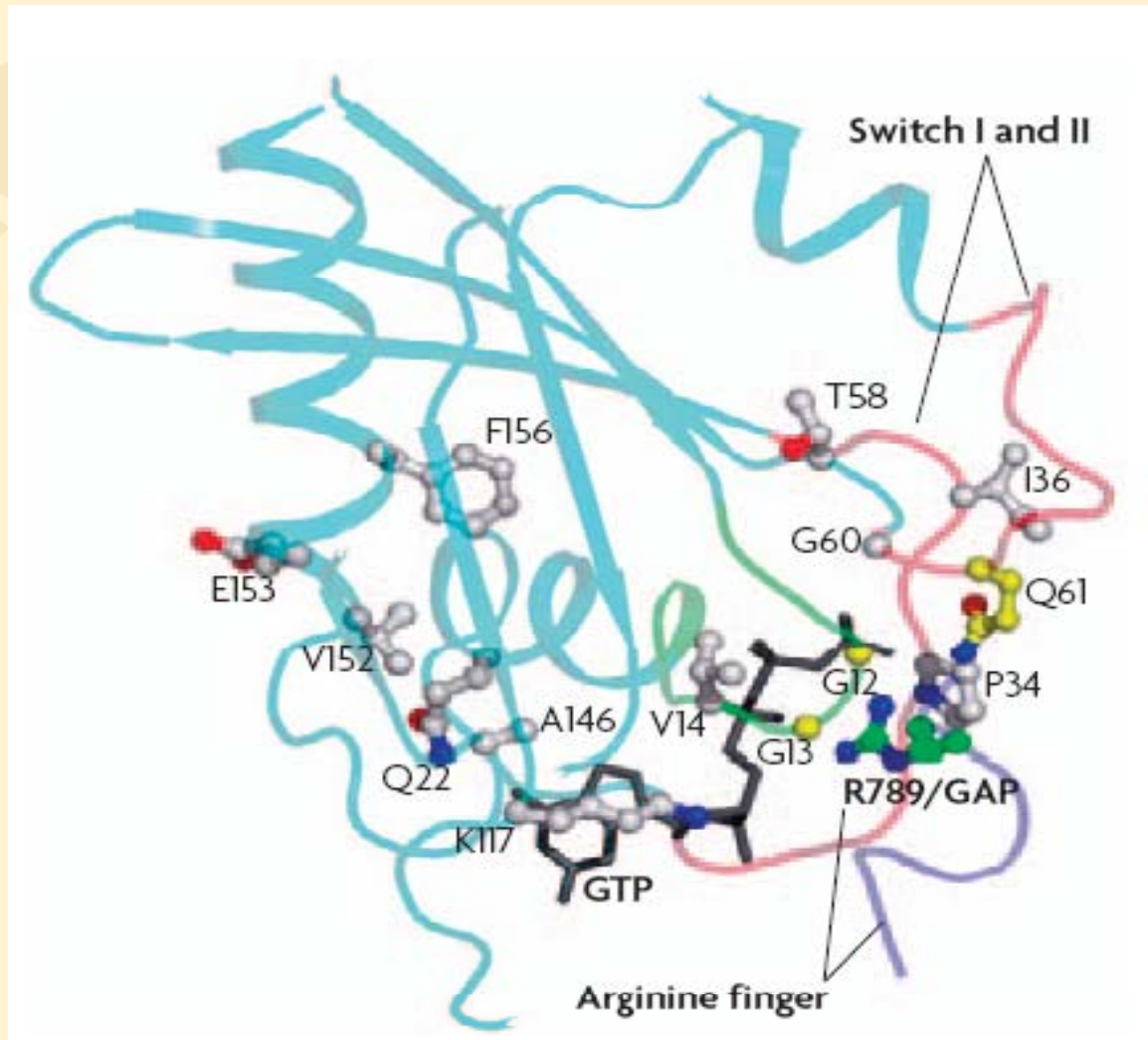
mutant KRAS: mutated KRAS protein (continuously sends signal to nucleus)

KRAS mutations occur frequently in colorectal cancer

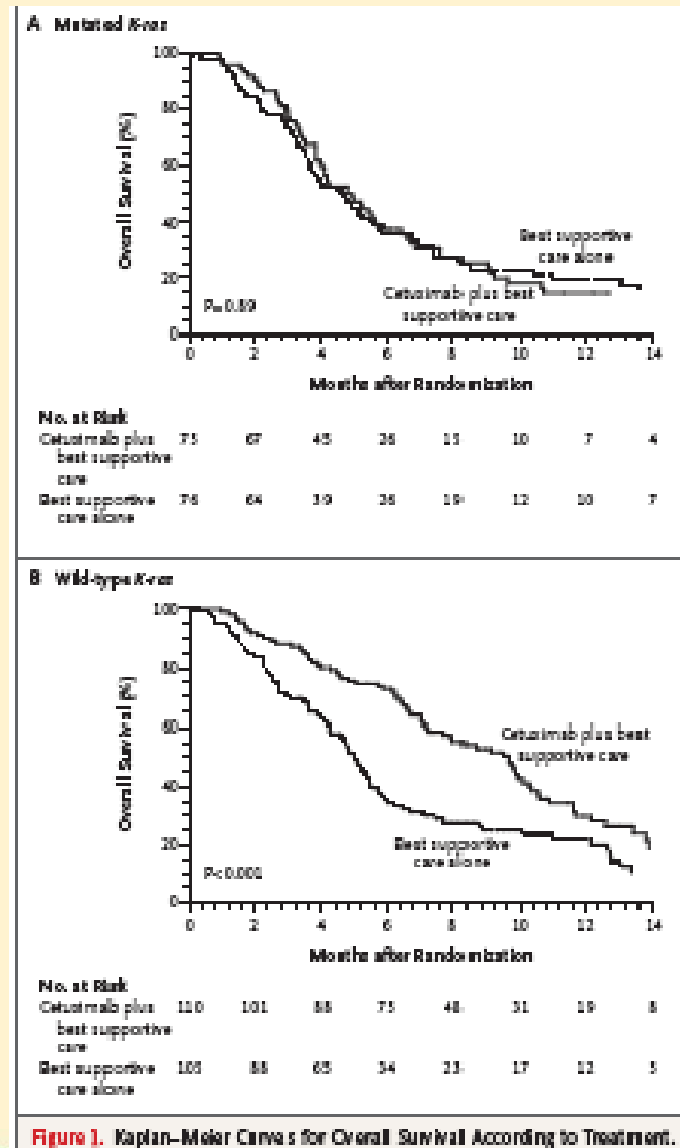
| Cancer type | HRAS | KRAS | NRAS | BRAF |
|-------------------|------|------|------|------|
| Biliary tract | 0% | 33% | 1% | 14% |
| Bladder | 11% | 4% | 3% | 0% |
| Breast | 0% | 4% | 0% | 2% |
| Cervix | 9% | 9% | 1% | 0% |
| Colon | 0% | 32% | 3% | 14% |
| Endometrial | 1% | 15% | 0% | 1% |
| Kidney | 0% | 1% | 0% | 0% |
| Liver | 0% | 8% | 10% | 3% |
| Lung | 1% | 19% | 1% | 2% |
| Melanoma | 6% | 2% | 18% | 43% |
| Myeloid leukaemia | 0% | 5% | 14% | 1% |
| Ovarian | 0% | 17% | 4% | 15% |
| Pancreas | 0% | 60% | 2% | 3% |
| Thyroid | 5% | 4% | 7% | 27% |

The mutation data was obtained from the [Sanger Institute Catalogue of Somatic Mutations in Cancer](#) web site¹⁴⁸.

The large majority of KRAS mutations occur in two amino acid “hot-spots” (Gly 12 and Gly 13)



- All survival benefit occurred in patients with K-ras wild type tumours
- No benefit at all in patients with K-ras mutated type
- Significant difference in treatment effects between the 2 groups ($p < 0.01$)
- K-ras now being routinely incorporated into practice for clinical practice and for future trials using therapies targeted at the EGFR receptor pathway



NEJM 2008; 359:1757-65

C0.17: Cost-effectiveness Analysis

Cost -effectiveness – all patients

| Component | Cetux | BSC | Difference |
|------------------------------|-----------------|----------------|------------------|
| Mean cost per patient | \$28,200 | \$4,200 | \$24,000 |
| Mean survival (LY) | 0.64 | 0.52 | 0.12 |
| Mean QALY | 0.40 | 0.32 | 0.08 |
| ICER | | | |
| \$ per LY | | | \$200,000 |
| \$ per QALY | | | \$300,000 |

Milman N et al JNCI 2009 (in press)











C0.17: Cost-effectiveness Analysis


Cost -effectiveness – K-ras wild type

| Component | Cetux | BSC | Difference |
|------------------------------|-----------------|----------------|------------------|
| Mean cost per patient | \$37,300 | \$3,700 | \$33,600 |
| Mean survival (LY) | 0.79 | 0.51 | 0.28 |
| Mean QALY | 0.51 | 0.33 | 0.18 |
| ICER | | | |
| \$ per LY | | | \$120,000 |
| \$ per QALY | | | \$190,000 |

Mittman N et al JNCI 2009 (in press)

International Cancer Genome Consortium

- [Brain Cancer](#)
United States 
- [Breast Cancer](#)
European Union / United Kingdom 
- [Breast Cancer](#)
France 
- [Breast Cancer](#)
United Kingdom 
- [Chronic Lymphocytic Leukemia](#)
Spain 
- [Colon Cancer](#)
United States 
- [Gastric Cancer](#)
China 
- [Leukemia](#)
United States 
- [Liver Cancer](#)
France 
- [Liver Cancer](#)
Japan 



[Show]

ICGC Goal: To obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different tumor types and/or subtypes which are of clinical and societal importance across the world.

work of cancer genome projects. Nature 464, 993-998 (15 April 2010)


[HTML](#)












ICGC Public Presentation April 15, 2010 : [PDF](#) | [PPT](#)

International Cancer Genome Consortium (ICGC) Goals, Structure, Policies and Guidelines : [HTML](#) | [PDF](#)


Members of the ICGC

Committed Projects to date: 21



- [Lung Cancer](#)
United States 
- [Lung Cancer](#)
United States 
- [Oral Cancer](#)
India 
- [Ovarian Cancer](#)
Australia 
- [Ovarian Cancer](#)
United States 
- [Pancreatic Cancer](#)
Australia 
- [Pancreatic Cancer](#)
Canada 
- [Pediatric Brain Tumors](#)
Germany 
- [Prostate Cancer](#)
Canada 
- [Rare Pancreatic Tumors](#)
Italy 
- [Renal Cancer](#)
European Union / France 

[Policies and Guidelines](#) 
International Cancer Genome Consortium

[Access to Data](#) 
Data Coordination Center

[Apply for Access to Controlled Data](#) 
Data Access Compliance Office

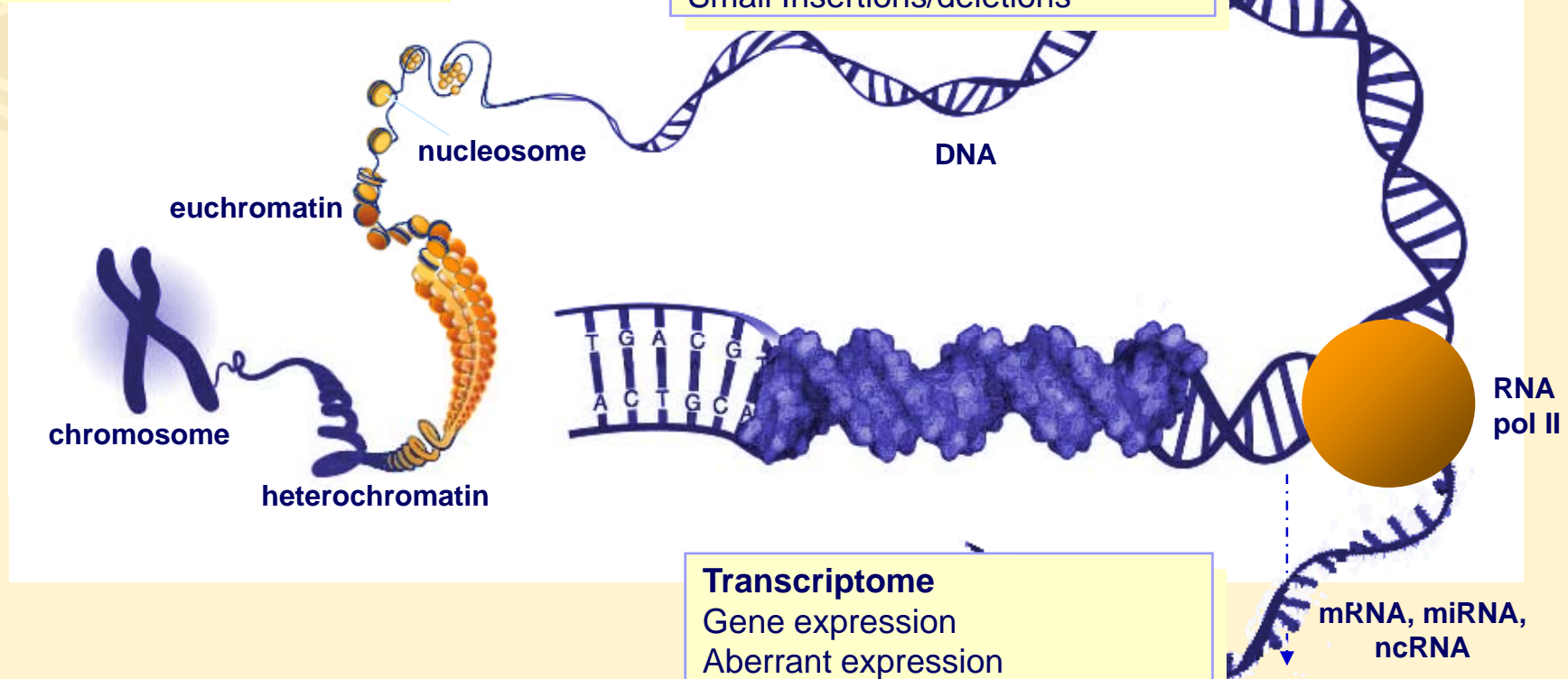
Molecular Events During Tumourigenesis

Epigenome:

Changes in DNA methylation
Histone modifications
Chromosomal instability

Genome

Chromosomal Organization
Copy Number Variation
Gene Fusion Event
Single Nucleotide Polymorphism
Small Insertions/deletions



Transcriptome

Gene expression
Aberrant expression
Altered miR –mRNA networks
Gene fusions
Expressed SNPs and mutations

Genome Sequencing



SNP/CNV Chip
analysis, gDNA
sequencing

Tumour & normal
gDNA

- 1) Profile matched DNAs on CNV/SNP array (Illumina 1M) and call ploidy and stromal gDNA contamination
- 2) Sequence fragment and long-mate pair libraries to a depth of 25 fold (75Gb)
- 3) Define Copy Number Variations
- 4) Define Structural Variations
- 5) Mine Single Nucleotide Variations
- 6) Mine insertion and deletions
- 7) Determine which events are somatic Vs germline
- 8) Benchmark calls against array data & validate leads
- 9) Collate all variants into the DCC

Returning Results

- Consideration must be made regarding return of results (NS section 3.5.1)
- Should not be an option for participants to decide yes or no at time of donation
 - How could they possibly know whether they do or do not want results?
- Researchers must not give results of any testing to individuals
 - Must be done by specialist genetic services
- There is no 'right' to results under Australian law



First case in Australia

- 35 year old male
 - Pancreatic cancer (has subsequently dies)
 - BRCA1/2 and PALB2 mutations
 - Has sisters
- What do we do?
 - S95/s95a/s95aa

DTC genetics

Genetic Testing for Health, Disease & Ancestry: DNA Test - 23andMe - Mozilla Firefox

File Edit View History Bookmarks Tools Help

23andme.com https://www.23andme.com/ 23 and me

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 **Choose to have it all.**
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News and Press
 [Introducing Relative Finder: Discover Relatives with Autosomal DNA](#)

Scientific Resources and Principles
Physician Resources
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Done

Start C:\Documents and... RPH 26-3-10-zeps Adobe Reader 100303 CoHT Issu... Genetic Testing f... 4:08 PM

Insurance Implications

- Duty to disclose
 - Should a participant tell their insurance company they are a part of a study?
 - No Australian moratorium
 - Uk has don't ask don't tell policy

Genetic testing for drug utility

- Do we need consent?
 - HER2/c-kit/bcr-abl
 - Oncocarta
 - Sub \$1000 WHG?
- Who Pays?
- How do you tell someone they aren't eligible for a 'wonderdrug'?



The screenshot displays the Sequenom website's product page for the OncoCarta Panel v1.0. The page is titled "Rare Mutation Profiling" and "OncoCarta Panel". It describes the panel as a "Comprehensive multi-gene panel for rare somatic mutation profiling". The text explains that recent studies suggest genetic variants play a significant role in tumorigenesis, pathogenesis, and disease progression. The OncoCarta Panel v1.0 is a ready-to-use panel for rapid discovery and validation of over 230 somatic mutations, ranging from single base changes to insertions and deletions of varying lengths, in key oncogenes including *EGRF*, *BRAF*, *KIT*, and *KRAS*.

Product Description

The OncoCarta™ Panel is the most comprehensive multi-gene panel available for profiling rare somatic mutations, enabling cancer researchers to rapidly profile genetic changes associated with tumor initiation and progression.

- Revolutionary—the only panel for rare somatic mutation analysis with 19 oncogenes and 238 mutations in 24 multiplexes
- Cutting Edge—detection as low as 10% mutation frequency in mixed tumor samples
- High quality, low frequency data—our oncogene panel includes data analysis and training by our expert scientific team
- Less than 500 nanograms DNA per sample—key when using FFPE samples
- Ready-to-go—run samples in your lab or send them our way for rapid results

Routine practice vs research

- Warren and Marshall project would be 'unethical' today
 - Clearly this is wrong
- For HFE and DMD what is the distinction between research and diagnostics?
- Until we have 'cure' every patient is a research participant

- Molecular pathology
 - raise ethical concerns
 - Need a proportional regulation framework

