Use of Human biospecimens

Dr Nik Zeps
Disclosures

- Employer:
  - SJOG HealthCare
  - DoHWA
  - DOHA (NHMRC, OGTR and Cancer Australia)

- Received funds from
  - Roche, AstraZeneca, Pfizer, Merck Serono, CSL

- Member of
  - AGITG, COSA, ABNA, ISBER, ASMR
Clinical Practice

Patients

Clinical Phenotyping

Treatment

Follow Up

Medical notes
- Diagnostic Tests
  - Pathology
  - Imaging
  - Genetics
- Medical History

• Standard
• Trial

Clinical Registries
Translational Research

- Requires access to well annotated human biological specimens
  - High quality
  - Validated
  - Sufficient numbers
  - Good clinical data and follow up
  - Consent
ProC Foundation Leukaemia and Lymphoma Tissue Bank

The ProC Foundation Leukaemia and Lymphoma Tissue Bank is a joint initiative of the Australian Leukaemia and Lymphoma Group (ALLG) and the Leukaemia Foundation. Australia's first and only haematological Tissue Bank in Australia, it was established in October 2002 with the generous assistance of ANZ Foundation.

The Tissue Bank is located in the Princess Alexandra Hospital in Brisbane and is managed by Dr. Paula Martin, founding Director of the Tissue Bank and former Chair of the ALLG Scientific Committee.

In late 2003, Pharmacia & Upjohn's Foundation became the naming rights sponsor of the Tissue Bank, continuing its strong support of the Leukaemia Foundation and our mission to finding better treatment and cure.

What is the Tissue Bank?
The ProC Foundation Leukaemia and Lymphoma Tissue Bank is a temperature-controlled facility for storing clinical tissue samples to be used in approved research. The samples are human tissue samples collected from the blood, bone marrow and other body organs of patients across Australia with a leukaemia, lymphoma, myeloma or related blood disorder. All the tissues are collected with the informed consent of the patients.

A central secure database has been established and maintained to facilitate rapid tracking of the resources within the bank and record sample use.

The central repository gives researchers access to accumulated tissue samples of blood disorders and enables research groups to conduct larger scale studies. Prior to the establishment of the Tissue Bank, it was difficult for researchers in Australia to access sufficient variety and numbers of tissue samples without an organised collection and storage process.

The Tissue bank therefore plays a crucial role in research into leukaemia and other blood cancer research which seeks to improve our understanding of:

- The biological processes leading to the development of these cancers
- The factors which control variable patient response to current treatments
- More effective therapies for patients
BBMRI during the transition phase

BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) was one of the first European Research Infrastructure projects funded by the European Commission (EC). The EC-funded preparatory phase of BBMRI came to its end in January 2011. During the past 3 years BBMRI has grown into a 33-member consortium with over 200 associated organisations (largely biobanks) from over 30 countries, making it the largest research infrastructure project in Europe. During the preparatory phase the concept of a functional pan-European biobank was formulated and has now been presented to Member States of the European Union and for associated states for approval and funding.

BBMRI will form an interface between specimen and data from patients and European populations and top-level biological and medical research. This can only be achieved through a distributed research infrastructure with operational units in all participating Member States. BBMRI will be implemented under the ERIC (European Research Infrastructure Consortium) legal entity. BBMRI-ERIC (receives headquarters (central coordination) in Graz, Austria, responsible for coordination of the activities of National Nodes established in participating countries. BBMRI is in the process of submitting its application to the European Commission for a legal status under the ERIC regulation, with an expected start date at the end of 2011.

When the preparatory phase of BBMRI came to its end on January 31, 2011, also the Governance and Management Structures which were based on the Grant Agreement came to end. In its final teleconference on Jan 26, 2011, the BBMRI Steering Committee agreed that the current Steering Committee will continue to function as an interim governing body of BBMRI until the Memorandum of Understanding (MoU) for the BBMRI-ERIC application is signed by the interested Member States. As BBMRI-ERIC will be an organization of Member States, Associated States, third countries and intergovernmental organizations, current biobanks that are partners or associated organizations of BBMRI and wish to become members of BBMRI-ERIC need to contact their ministries and encourage them to seek membership under the new legal entity.

The next ministerial level meeting organized by the Austrian ministry will take place in Graz, Austria, on March 26-27, 2011. If the ministry of your country is interested to participate in this meeting, but has not received an invitation, please contact Dr. Hermann Bauer (hermann.bauer@bmvit.gv.at).
Pathology services

- Primary role is diagnosis
  - Surgical resections
  - Biopsies
  - ‘Waste’ blood
  - Mortuary
- Legislated to keep samples for QA
- Performance management means no money for biobanking
  - Research not part of the new culture
- No consent
- Academic pathology in decline
- Often regarded as a ‘larder’ by researchers
What is Human Tissue?

- Body parts
- Whole organs
- Tissue blocks & slides
- Cells
- Bio-fluids, hair
- Proteins, lipids, nucleic acids, etc

No consistent definitions in laws/guidelines but we must comply with them all.
Follow up

- How comprehensive is it?
- How reliable is it?
- How long is follow up?
- Time to recurrence outside of a clinical trial is mythology
Pathology Labs: Concerns

- Is there spare tissue?
- Can you have access to diagnostic samples?
  - Who owns tissue?
  - What are legal obligations?
What is your sample?

- Needs pathologist review
- Tumour content important?
- Access to follow up reports?
- Access to full diagnostic testing?
Public trust: The result of good ethical research

But....
The Havasupai Indian Tribe Case — Lessons for Research Involving Stored Biologic Samples
Michelle M. Mello, J.D., Ph.D., and Leslie E. Wolf, J.D., M.P.H.

On April 20, 2010, Arizona State University (ASU) agreed to pay $700,000 to 41 members of the Havasupai Indian tribe to settle legal claims that university researchers improperly used tribe members' blood samples in genetic research. The settlement closes a difficult chapter for both parties but leaves open a bedeviling question for genetic research: What constitutes adequate informed consent for biospecimens collected for research to be stored and used in future, possibly unrelated studies? The case illuminates the clashing values that have driven debate in this area and the importance of understanding the study population's perspectives.

The Havasupai suit stemmed from a 1990 diabetes study in behavioral/medical disorders, but prestudy communications with tribal leaders apparently focused on diabetes. The researchers used the samples in multiple studies unrelated to diabetes, sharing them with other investigators. Tribe members particularly objected to three uses: a study evaluating the genetic basis of schizophrenia, which could stigmatize the tribe; one examining inbreeding, which raised stigmatization issues and concern related to a cultural belief that inbreeding brings harm to one's health; and a study evaluating the genetic basis of diabetes, which could lead to genetic discrimination. The Havasupai faced an uphill battle, since other plaintiffs who have asserted their rights to control the use of research specimens have generally been unsuccessful.

In 2004, tribe members filed a $50 million lawsuit alleging, among other things, fraud, breach of fiduciary duty, negligence, and trespass. The core legal question was whether the downstream uses of the samples fell within the scope of the donors' informed consent. The Havasupai faced an uphill battle, since other plaintiffs who have asserted their rights to control the use of research specimens have generally been unsuccessful.

However, after several years of legal wrangling, ASU agreed to settle. In addition to providing monetary compensation, ASU formally apologized and agreed to work with the tribe on issues of health, education, and economic development. ASU also agreed...
Henrietta Everlasting: 1950s Cells Still Alive, Helping Science
By Erin Bibe  January 25, 2010  12:00 pm  |  Wired Feb 2010

In 1951, an African-American woman named Henrietta Lacks went to Johns Hopkins Hospital to be treated for cervical cancer. Unbeknownst to her, cells from her biopsy were made available to biomedical researchers.

Lacks died a year later, but her cells — known as HeLa — live on. A fast book by Rebecca Skloot, The Immortal Life of Henrietta Lacks, examines the extraordinary impact of HeLa cell science and the effects of that unfinished legacy on Lacks’ family. Here’s a look at a most eventful afterlife.

10 Popular Cell Lines for Research

HeLa is not the only cell line in use today. Thousands have found their way into labs worldwide. Here are some commonly used lines and the number of scientific papers they appear in.

Number of Scientific Papers

[Diagram showing areas of discovery with years and genes]
Guidelines for Biobanks/databanks

- National Statement
- Privacy Act
- NATA/NPAAC
- ISBER Best Practices Manual
- NHMRC-HGAC Biobanks Information Paper
- OECD Biobanks paper
  - *Guidelines for Human Biobanks, Genetic Research Databases & Associated Data*
Why do we ask for consent?

- **Respect** (NS 1.10)
- Expression of Autonomy
  - empowerment
- Altruism
- Compliance with guidelines/legal requirements
Consent

- How much should the participant understand?
- What do we mean by ‘informed’ consent?
  - Poly-omic research?
  - Gene lists?
# WA Research Tissue Network Consent Form

**Surnames:**

**Forenames:**

**Sex:**

**DOB:**

---

**Consent for tissue/blood taking and tissue/blood banking for clinical research**

I, ________________________ of ______________________________________________ have read the Information Brochure entitled “WA RESEARCH TISSUE NETWORK”, (Doctor or health professional) ……………………………….. has explained to me and I understand the consequences involved in my voluntary donation of tissue and/or blood for the WA Research Tissue Network. I have had an opportunity to ask questions and am satisfied with the answers given.

In making my donation, I understand and agree that:

1. the tissue/blood (which in this consent form, includes its constituents and any cell lines derived from the tissue/blood) will be used in relation to [WRITE IN PROJECT NAME],
2. samples of any tissue/blood or derived cell line(s) held in a bank will be discarded upon my written request to the WA Research Tissue Network Project Manager,
3. the results of research studies are deemed experimental and not for diagnostic purposes and therefore not intended to be passed back to me or my immediate family,
4. I wish/ do not wish to be informed of important general results and the progress of any study through a newsletter which will contain information about these studies in a form that will not allow individuals to be identified,
5. I can request to know more specific details of any studies that used my samples at any time by contacting the WARTN,
6. Research results, and the fact that I have made this donation, will not be revealed to any 3rd party not directly part of medical research without my written consent, except under subpoena ,
7. The WA Research Tissue Network will not be liable for any loss of or damage to, the tissue/blood used in accordance with this form,
8. I will not benefit financially if this research leads to development of a new treatment or medical test,
9. storage of and access to my tissue/blood will be managed by an Advisory Committee and only released where the research proposal has been approved by a Human Research Ethics Committee,
10. I understand that international research collaboration using my tissue/blood will only take place where researchers abide by equal or more stringent regulations of privacy and ethics as those in Australia, as assessed by a Human Research Ethics Committee,
11. I give permission to access health information about me related to the research area defined in point 1 above, such as is kept in a medical record or by the WA Department of Health, to assist medical research only where the research proposal has been approved by a Human Research Ethics Committee.

I ______ Do ______ Do Not ______ consent to the storage and use of my tissue and/or blood (delete as appropriate) for biochemical and genetic based medical research.

<table>
<thead>
<tr>
<th>Name of Patient</th>
<th>Signature of Patient</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>……………………………………………………………………………………</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of Doctor</th>
<th>Signature of Doctor</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>……………………………………………………………………………………</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
Why does Biobanking Matter?

- We don’t have cures for all diseases
- We don’t classify disease properly still
- Novel preventions and treatments depend upon better biological understanding
Emerging Molecular Taxonomy
Potentially many low prevalence phenotypes
Molecular Taxonomy – Cancer “Biotypes”

- Estrogen Dependent
- Abl-like Kinase Dependant
- EGFR dependent
- HER2 Amplified
- ALK
- Homologous Recombination Defective
- BRAF mutant
- NOVEL mutant
Anatomy and histology

Image adapted from http://wn.com/colon_cancer

Image adapted from Department of health WA website.
Tumours arise at different sections of the colon have different molecular features and they respond to treatment differently.

**Proximal**
- p53+ = 30%
- MSI+ = 25%
- TS = 22%
- CIMP+ = 20-30%
- KRAS = 40%
- BRAF = 17%
- dMMR = 26%

**Distal**
- p53+ = 60%
- MSI+ = 3%
- TS = 56%
- CIMP+ = 5-10%
- KRAS = 28%
- BRAF = 2%
- dMMR = 3%

**Graphical Representation**

- TC
- AC
- DC
- C
- R
- SC

KRAS = 36%
BRAF = 2%
dMMR = 1%
**Tissue Based Assays**

<table>
<thead>
<tr>
<th>Method</th>
<th>ISH</th>
<th>HER2</th>
<th>EML4-ALK</th>
<th>LKB1</th>
<th>PTEN</th>
<th>Ph-Src</th>
<th>Ph-EGFR</th>
<th>Ph-mTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter: 27 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Margins: MC 2mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN: 3 of 24 POS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PN inv: POS</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSI inv: POS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Targeted IVDs**

<table>
<thead>
<tr>
<th>Method</th>
<th>Expression Arrays</th>
<th>Methylation Arrays</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR sequencing</td>
<td>EXPRESSION Arrays</td>
<td>METHYLATION Arrays</td>
</tr>
<tr>
<td>EGFR</td>
<td>PROGNOSIS POOR</td>
<td>PREDICTIVE NIL</td>
</tr>
<tr>
<td>KIT</td>
<td>PREDICTIVE</td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>anti-EGFR NEG</td>
<td></td>
</tr>
<tr>
<td>STK11</td>
<td>CUSTOM Assays</td>
<td></td>
</tr>
<tr>
<td>SNP Arrays</td>
<td>Tissue of Origin</td>
<td></td>
</tr>
<tr>
<td>HER2 amplified</td>
<td>PROGNOSIS POOR</td>
<td></td>
</tr>
</tbody>
</table>

**Whole Genome**

<table>
<thead>
<tr>
<th>Tumour Cellularity</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequencing Depth</td>
<td>40x N / 200x T</td>
</tr>
<tr>
<td>Copy Number Variations</td>
<td>15,140</td>
</tr>
<tr>
<td>% of Genome Affected by CNV</td>
<td>6.1%</td>
</tr>
<tr>
<td>Inter-Chromosomal Translocations</td>
<td>3</td>
</tr>
<tr>
<td>Homozygous Loss</td>
<td>CDK2NA</td>
</tr>
<tr>
<td>LOH:</td>
<td>BRCA2, TP53, SMAD4</td>
</tr>
</tbody>
</table>

**Non-Synonymous Somatic Mutations**

- **gene**
  - KRAS
  - TP53
  - SMAD4
  - LML3
  - BRAF
  - TGFBR2
  - CTNNA2
  - PCDH15

- **aa change**
  - G12D
  - R273H
  - Q248*
  - K1518I
  - V600E
  - R495*
  - V448D
  - R528T

- **exome expressed**
  - Yes
  - No

**Significant Germline Mutations**

- **gene**
  - BRCA2
  - K3326*

- **aa change**
  - K3326*

- **exome expressed**
  - Yes
  - No
Histopathology: Losing a loser

Pre-dose

Post-dose

Convincing biological activity

Maximum Tolerated Single dose
In volunteers

Maximum Tolerated Repeat dose
In patients

Kill
Failure to select BM/target + patients will adversely impact on power

Power declines dramatically as the fraction of pts with target decreases.
NCI C / AGITG Trial CO.17:
Randomized Phase III Trial in mCRC
Failed or intolerant to all recommended therapies

**EGFR testing by IHC**

Stratification:
- Centre
- ECOG PS (0 or 1 vs. 2)

**Cetuximab* + BSC**

* Cetuximab 400 mg/m² IV week 1 then 250 mg/m² IV weekly

**BSC alone**

Disease Progression or Unacceptable Toxicity
NCIC / AGITG CO.17: Overall Survival

HR 0.77 (95% CI = 0.64 – 0.92) (p-value = 0.0046)

<table>
<thead>
<tr>
<th>Study arm</th>
<th>MS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + BSC</td>
<td>6.1</td>
<td>5.4 - 6.7</td>
</tr>
<tr>
<td>BSC alone</td>
<td>4.6</td>
<td>4.2 - 4.9</td>
</tr>
</tbody>
</table>

Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>CET+BSC</td>
<td>287</td>
<td>217</td>
<td>136</td>
<td>78</td>
<td>37</td>
<td>14</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BSC</td>
<td>285</td>
<td>197</td>
<td>85</td>
<td>44</td>
<td>26</td>
<td>12</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
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

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

The mutation data was obtained from the Sanger Institute Catalogue of Somatic Mutations in Cancer web site.
NCI C CTG CO.17 K-Ras Analysis

N=572 randomized: ITT subset

N=394: K-ras assessed subset (69%)

N=164 (42%) mutant

N=230 (58%) wild-type

- Genomic DNA extracted from FFPET slides or sections
- Assessed by bidirectional sequencing for codon 12/13 mutations
- No difference between K-ras mutated and WT patients re: demographics, previous treatment or other variables
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.
KRAS Mutations Predictive But Not Prognostic in Colorectal Cancer

Median Progress-Free Survival (PFS)

<table>
<thead>
<tr>
<th>KRAS Mutation</th>
<th>PFS With Cetuximab and FOLFRI (Months)</th>
<th>PFS With Best Supportive Care (Months)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3.8</td>
<td>1.9</td>
<td>0.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>1.8</td>
<td>1.8</td>
<td>0.99</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Median Overall Survival (OS)

<table>
<thead>
<tr>
<th>KRAS Mutation</th>
<th>OS With Cetuximab and FOLFRI (Months)</th>
<th>OS With Best Supportive Care (Months)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>9.5</td>
<td>4.8</td>
<td>0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>4.6</td>
<td>4.5</td>
<td>0.98</td>
<td>0.89</td>
</tr>
</tbody>
</table>
## C0.17: Cost-effectiveness Analysis

Cost-effectiveness – all patients

<table>
<thead>
<tr>
<th>Component</th>
<th>Cetux</th>
<th>BSC</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cost per patient</td>
<td>$28,200</td>
<td>$4,200</td>
<td>$24,000</td>
</tr>
<tr>
<td>Mean survival (LY)</td>
<td>0.64</td>
<td>0.52</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean QALY</td>
<td>0.40</td>
<td>0.32</td>
<td>0.08</td>
</tr>
<tr>
<td>ICER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$ per LY</td>
<td></td>
<td></td>
<td>$200,000</td>
</tr>
<tr>
<td>$ per QALY</td>
<td></td>
<td></td>
<td>$300,000</td>
</tr>
</tbody>
</table>

Mittman R et al JNCI 2009 (in press)
# C0.17: Cost-effectiveness Analysis

## Cost-effectiveness - K-ras wild type

<table>
<thead>
<tr>
<th>Component</th>
<th>Cetux</th>
<th>BSC</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean cost per patient</td>
<td>$37,300</td>
<td>$3,700</td>
<td>$33,600</td>
</tr>
<tr>
<td>Mean survival (LY)</td>
<td>0.79</td>
<td>0.51</td>
<td>0.28</td>
</tr>
<tr>
<td>Mean QALY</td>
<td>0.51</td>
<td>0.33</td>
<td>0.18</td>
</tr>
<tr>
<td>ICER $ per LY</td>
<td></td>
<td>$120,000</td>
<td></td>
</tr>
<tr>
<td>ICER $ per QALY</td>
<td></td>
<td>$190,000</td>
<td></td>
</tr>
</tbody>
</table>

*Mittman N et al JNCI 2009 (in press)*
Genetic Information (3.5)

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

RNA pol II
mRNA, miRNA, ncRNA
ICGC Ethics and Policy Committee

**Mandate**

- The Ethics and Policy Committee (EPC) is responsible for:
  - examining and raising issues of consent,
  - privacy protection,
  - data access,
  - ethical and legal topics relevant to the International Cancer Genome Consortium (ICGC).

- The EPC will draft recommendations and policy statements or guidelines.
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
Insurance Implications

- Duty to disclose
  - participation?
- Right to know?
  - Calculate risk
- Accuracy?
  - gene-environment
  - Randomness
- Shutting the gate
disease risk

To ensure that the information on this page is as accurate as possible, please set your ancestry on your profile page.

Show results for

See new and recently updated reports

23andMe Discoveries were made possible by 23andMe members who took surveys.

Elevated Risk

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Your Risk</th>
<th>Avg. Risk</th>
<th>Compared to Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>★★★★★</td>
<td>37.3%</td>
<td>17.0%</td>
<td>2.09x</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>★★★★★</td>
<td>33.9%</td>
<td>27.2%</td>
<td>1.25x</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>★★★★★</td>
<td>7.5%</td>
<td>5.6%</td>
<td>1.30x</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>★★★★★</td>
<td>6.5%</td>
<td>6.5%</td>
<td>1.00x</td>
</tr>
<tr>
<td>Scleroderma (Limited Cutaneous Type)</td>
<td>★★★★★</td>
<td>6.08%</td>
<td>6.07%</td>
<td>1.00x</td>
</tr>
<tr>
<td>Alcohol Dependence</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer's Anxiety</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Cell Carcinoma</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder Disorder, Preliminary Research</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac Disease, Preliminary Research</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glaucoma, Preliminary Research</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klinefelter</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson's Disease, Preliminary Research</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>★★★</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Decreased Risk

<table>
<thead>
<tr>
<th>Name</th>
<th>Confidence</th>
<th>Your Risk</th>
<th>Avg. Risk</th>
<th>Compared to Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>35.3%</td>
<td>48.8%</td>
<td>0.75x</td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>19.9%</td>
<td>25.7%</td>
<td>0.77x</td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s Disease</td>
<td>4.6%</td>
<td>7.2%</td>
<td>0.86x</td>
<td></td>
</tr>
<tr>
<td>Age-related Macular Degeneration</td>
<td>3.3%</td>
<td>6.5%</td>
<td>0.59x</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>1.5%</td>
<td>2.4%</td>
<td>0.28x</td>
<td></td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>1.5%</td>
<td>2.5%</td>
<td>0.74x</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>0.7%</td>
<td>2.3%</td>
<td>0.26x</td>
<td></td>
</tr>
<tr>
<td>Esophageal Adenocarcinoma</td>
<td>8.6%</td>
<td>0.7%</td>
<td>0.79x</td>
<td></td>
</tr>
<tr>
<td>Esophageal Squamous Cell Carcinoma (ESCC)</td>
<td>8.3%</td>
<td>0.4%</td>
<td>0.90x</td>
<td></td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>8.2%</td>
<td>0.3%</td>
<td>0.95x</td>
<td></td>
</tr>
<tr>
<td>Stomach Cancer (Gastric Cardia Adenocarcinoma)</td>
<td>8.2%</td>
<td>0.2%</td>
<td>0.77x</td>
<td></td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>6.6%</td>
<td>1.5%</td>
<td>0.66x</td>
<td></td>
</tr>
<tr>
<td>Colonic Disease</td>
<td>6.6%</td>
<td>0.12%</td>
<td>0.63x</td>
<td></td>
</tr>
<tr>
<td>Brain Aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Cancer Risk Modifiers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster Headaches</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease: Preliminary Research</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney Stones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lou Gehrig Disease (ALS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: The table entries represent the risk reduction compared to the average risk.*
Prostate Cancer

Established Research report on 12 reported markers, updated November 4th, 2010.

About Prostate Cancer

Prostate cancer is by far the most common cancer affecting men. (Women don't have prostate glands and therefore cannot get prostate cancer, but can pass markers to their children.) About one in six men will develop prostate cancer over their lifetimes, according to the American Cancer Society. Fortunately, most prostate tumors grow slowly, and if detected early, treatment may help control their size. Until recently, the only well-known risk factors for prostate cancer were age, ethnicity, and family history. Although advanced age increases a person's risk for any type of cancer, the involvement of ethnicity and family history suggests that there is a strong genetic component as well.

Learn more about the biology of Prostate Cancer...

Major discoveries in Prostate Cancer...

Your Genetic Data

Nik Zeps

37.3 out of 100

men of European ethnicity who share Nik Zeps' genotype will develop Prostate Cancer between the ages of 55 and 75.

Average

17.8 out of 100

men of European ethnicity will develop Prostate Cancer between the ages of 55 and 75.

What does the Odds Calculator show me?

Use the ethnicity and age range selectors above to see the estimated incidence of Prostate Cancer due to genetics for men with Nik Zeps' genotype. The 23andMe Odds Calculator assumes that a person is free of the condition at the lower age in the range. You can use the name selector above to see the estimated incidence of Prostate Cancer for the genotype of other people in your account.

The 23andMe Odds Calculator only takes into account effects of markers with known associations that are tested on our genotyping chip. Keep in mind that aside from genetics, environment and lifestyle may also contribute to one's risk for Prostate Cancer.
What You Can Do

Assuming the ethnicity testing above is correct, your test results indicate you are at increased risk for prostate cancer based on genetics. Note that family history, non-genetic factors and genetic factors not covered in this report can also influence your risk for prostate cancer. There are, however, steps you can take to reduce your risk.

Talk to your doctor about screening tests
The American Cancer Society recommends that men make the decision about whether or not to be tested for prostate cancer in consultation with their doctors. Research has not yet proven that the potential benefits of testing outweigh the harms of testing and treatment.

- Starting at age 50, talk to your doctor about the pros and cons of testing.
- If you are African American or have a father or brother who had prostate cancer before age 65, you should have this talk with your doctor starting at age 45.
- If you decide to be tested, you should have the PSA blood test with or without a rectal exam. Testing frequency will depend on your PSA level.

Estimate your risk
Use the questionnaire available from Your Disease Risk, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine to get an estimate of your risk for prostate cancer.

Tomatoes can’t hurt, but...
According to the National Cancer Institute, studies of whether a diet high in lycopene (the bright red pigment found in tomatoes and other red fruits & vegetables) is linked to a decreased risk of prostate cancer have been inconclusive. It has also not been proven that taking lycopene supplements decreases the risk of prostate cancer.

Get enough folate in your diet
The National Cancer Institute describes a 16-year study that showed that the risk of prostate cancer was reduced in men who had enough folate (a B vitamin) in their diets. But the risk was increased in men who took supplements of folate acid, which is the synthetic form of folate.

Moderate calcium intake
Some research has indicated that taking large doses of calcium supplements or having a high intake of dairy products increases the risk for prostate cancer. But calcium is important for bone health and may play a role in preventing other cancers, so moderation, not complete avoidance of calcium, is recommended.

Learn your family medical history
The Centers for Disease Control and Prevention say that a man with a father, brother, or son who has had prostate cancer is two to three times more likely to develop the disease himself. The U.S. Surgeon General’s My Family Health Portrait tool can help you collect the information you need.

Connect with relevant groups
- American Cancer Society
  800-ACS-2345
- Prostate Cancer Foundation
  800-797-CURE
**Marker Effects**

What does this chart show?

The chart shows the approximate effects of the selected prostate genotype at the 12 reported markers. Higher, red bars indicate increased risk from the average, while lower, green bars indicate decreased risk from the average. The light gray bars show the maximum possible effects for the possible genotypes at the marker.

Mouse over individual bars to view additional information about each marker. Click on a bar to view detailed information about that marker below. You can read more about all markers in the technical report.

### 8q24 (region 1)

**Marker:** rs1447395

Three SNPs in the same area of the genome have recently been found to be independently associated with prostate cancer risk. This region is called 8q24, because it lies within band 24 on the long arm (the "q" arm) of chromosome 8. The three SNPs are not close to known genes (although these are other loci located further away). But other studies have looked at DNA from prostate tumors and found that in the cancerous cells, this area of the genome often has unusual duplications, or extra copies of DNA.

The duplications might contribute to the progression of prostate cancer (for example, by increasing the number of genes related to cell growth), or they might simply be a side effect of the high mutation rate seen in all types of cancer cells. Similarly, the risk-associated versions of the SNPs in the 8q24 region might already affect activity levels of genes involved in prostate cancer, or they might somehow make it easier for DNA duplications to occur. (And, if they might only be linked to yet-unknown SNPs that are already involved.)

One study has investigated this association in Japanese Americans. Although the SNP also appears to be associated with prostate cancer risk in this population, evidence suggests that the extent of this SNP on risk may differ between populations. Therefore, the exact association in populations with Asian ancestry still needs to be confirmed.

### Citations

Our findings show that such an approach does not completely conceal identity, since it is straightforward to assess the probability that a person or relative participated in a GWA study.

greater emphasis is needed for providing mechanisms to confidentially share and combine individual genotype data across Studies.

Motive
Opportunity
Means
Job candidates getting tripped up by Facebook
many students learn the hard way that online
image can limit opportunity

By Wei Du msnbc.com updated 1:30 p.m. ET Aug. 14, 2007

Van Allen runs a company that recruits job candidates for hospitals and clinics across the country. With physicians in short supply, he was happy to come across the resume of a well-qualified young female psychiatrist. As part of his due diligence check, Allen looked her up in Facebook, a popular social networking Web site, and found things that made him think twice. “Pictures of her taking off her shirt at parties,” he said. “Not just on one occasion, but on another occasion, then another occasion.”
Commercialisation

Should anyone be allowed to make $$ out of selling the human body?

Do patients have an interest in trade or discovery?

NHMRC paper on Commercialisation of Human Tissue Products
- Release sept 2011
- Guidelines in revised 3.4

Trade in human tissue products
Nicholas Toni-Filippini and Nikola Zeps

ABSTRACT
- Trade in human tissue in Australia is prohibited by state law, and in ethical guidelines by the National Health and Medical Research Council:
  - National statement on ethical conduct in human research;
  - Organ and tissue donation by living donors: guidelines for ethical practice for health professionals;
- However, trade in human tissue products is a common practice especially for:
  - Reconstructive orthopaedic or plastic surgery;
  - Novel human tissue products such as replacement tissues created by using human mesenchymal stem cells;
  - Biomedical research using cell lines, DNA and proteomics provided through biobanks;
- Cost pressures on these have forced consideration of commercial models to sustain their operations. Both the existing and novel activities require a robust framework to enable commercial uses of human tissue products while maintaining community acceptability of such practices, but to date no such framework exists.
- In this article, we propose a model ethical framework for ethical governance which identifies specific ethical issues such as:
  - Privacy;
  - Unique value of a person's tissue;
  - Commodification of the body;
  - Equity and benefit to the community;
  - Perverse incentives; and
  - "Impressionism" as a potentially useful concept to help deal with the broad range of subjective values relevant to whether it is acceptable to commercialise certain human tissue products. 

A major concern is that if a laissez-faire situation persists in relation to human tissue products, then ownership may be the paradigm for tissue products and the ethical issues may only be resolved through case law when tested in court. Unfortunately, legal judgments accepting unseemly ownership could endanger the social capital that exists in the donation of human tissue for transplantation and research in Australia. Such a risk is in particular concern for organisations like blood, bone marrow and eye banks, and for solid organ transplantation programs which depend on goodwill. This goodwill may be threatened if the commercial industry in human tissue products is seen to be operated in a way that is not consistent with the wishes or values of the donors. Donors of human tissue typically presume that the issue will be used for the benefit of the community through transplantation and research, rather than for profit to individuals. Thus, decisions by courts to enforce ownership would be controversial, and could
Revision to 3.4/3.6

- Combine the two chapters
- New title “Biospecimens”
- Focus is on consent, identifiability and risk to donor.
- Targeted consultation finished
- Public consultation in October