Genomic Medicine in the Digital Age

4th International Digital Curation Conference
2nd December, 2008

Professor David J Porteous
Molecular Medicine Centre
The Appliance of Genetic Science

How our genetic history affects our health outcomes
Our Changing Demography

Scotland 1911

Scotland 1951

Scotland 2001

Scotland 2031
The rise and rise of chronic disease

- Stroke
- Diabetes
- Heart disease
- Cancer
- Dementia
- Arthritis
the Grim Reaper’s road map
An atlas of mortality in Britain

Mary Shaw, Bethan Thomas,
George Davey Smith and Daniel Dorling
Cancer, Heart & Lung Disease
Environmental Risk Factors
Nurture

- Stroke
- Diabetes
- Heart disease
- Cancer
- Dementia
- Arthritis
- Mental health
Nature

- Stroke
- Diabetes
- Heart disease
- Cancer
- Dementia
- Arthritis
- Mental health
Nurture and Nature
The Relative Risk in Relatives

How our genetic history affects our health outcomes
For better or for worse

The throw of the genetic dice
DNA: the stuff of life
1953: Watson & Crick Solve the Structure of DNA
Fifty Years On

2003: The Complete Human Genome Sequence
All 3,000 million G, A, T, C letters
All 30,000 genes
The throw of the genetic dice

G, A, T or C?

99.9% identical

0.1% different

Individual Variation & Disease Liability
Disease Gene Hunting

Glazier, Nadeau & Aitman, Science, 2002

The graph shows the number of human Mendelian traits for which the molecular basis has been found, along with all complex traits and human complex traits, from 1980 to 2000. The number increased significantly over the years, particularly for human complex traits.
How Specific Gene Variants Associate with Particular Diseases

Genome Wide Association Studies

- Very large scale studies of common diseases
- Comparing thousands of individuals with and without a given disease
- Up to $10^6$ variants per person
- Looking for frequency differences in DNA sequence variants between cases and controls
- Over 100 risk factors discovered
- But still some way to go
Genome Sequencing Technology Drive

1990-2003
- thousands of researchers
- several sequencing factories
- $3 billion

Now
- 1 machine
- a small team of researchers
- A few weeks
- $500,000

Next Year
- $5,000

Soon
- $1,000
The $5000 Genome

www.completegenomics.com

- 1,000 complete human genome sequences in 2009 @ $5000 each
- 20,000 in 2010
- 60,000 processors with 30 petabytes of storage
Multiple sequence alignments, comparative genomics & gene annotation = Bioinformatics

Evolution, Biology & Medicine
Putting it all together

Optimised patient prescription

Pharmacogenetics /genomics

Rational drug design

Drug Discovery Pipeline

Screening
Surveillance
Targeted treatment
Treatment choice

Altered DNA Sequence

Biology of Gene Product

Pharmacogenetics
Adverse Drug Reaction

- 4th leading cause of US hospital based mortality
- Affects 7% of NHS patients or hospital admissions
- Annual UK cost >£400 million
- Cost of bringing one new drug to market each year

- Personalised Medicine / Pharmacogenomics
  - choosing the right drug, first time
    - 30% respond
    - 30% don’t take it
    - 30% don’t respond
    - 10% respond badly
The Clinical Phenotype

- Signs & symptoms
- Pathology
- Physiology
- Biochemistry
- Scanning & Imaging

- Genotypes
- Expression profiles
- Biomarkers
- Molecular sensing
- Molecular imaging

- Natural Product
- Novel Chemical Entity (NCE)

- Biologics
- Rational Chemical Entity (RCE)

Pharmacologic Intervention
An Integrated Chemical Biophysics Screening Platform (Manfred Auer)

Library Chemistry  Preparation  Confocal scanning  Evaluate→hit wells  Hit-bead retrieval

Optical information, high sensitivity

Single molecule, Single cell spectroscopy & 400,000 compounds/day
A family & population based study of health & disease

‘It’s in the family: My auntie had it and so did my granddad. Now my brothers gone down with it. What about me and my children?'
Our Competitive Advantage

- Scottish people & culture
  - Unhealthy, Supportive & Stable Population
  - Large scale family based studies possible

- Academic networks of excellence
  - Clinical Research Facility Pipeline
  - Health Informatics
  - Genomic Science
  - Ethical, Legal & Social Science

- NHS Scotland
  - Disease Registers
  - ‘Cradle to Grave’ Health Records
Generation Scotland
Scottish Family Health Study

A family based, volunteer study of gene predictors of disease & well being
A typical Scottish Family...
A Real Generation Scotland Family
19 volunteers (3 generations: 17 clinic appointments and 2 postal contributions)

F26 (Proband) = 8 genetic links  
M18 (cousin) = 10 genetic links  
F78 (grandmother) = 9 genetic links  
M25 (cousin) = 11 genetic links
Where

- Banff
- Peterhead
- Aberdeen
- Dundee
- Glasgow
- Edinburgh
- Peterhead
State-of-the-art Clinical Research Facilities

- Wellcome Trust Clinical Research Facility
- BHF Cardiovascular Research Centre
- Biomedical Research Centre
- Institute of Medical Sciences

Edinburgh
Glasgow
Dundee
Aberdeen
Pre-clinic Questionnaire

- Demographic details
- Lifestyle and occupational history
- Personal and family medical history
Clinic Visit

Biological samples

- Blood sample for DNA & biochemistry
- Serum & urine for proteins and metabolites
Clinic Visit
Health related measurements

- Height
- Weight
- Waist-hip ratio
- Blood Pressure
- Lung capacity
- Heart function
- Bone density
- Cognitive function
- Mental Health

Kg
Mental Health

- ~450 million affected by mental disorder
- ~10% of global adult population
Antidepressants & Antipsychotics

- Positive impact on patients, but...
- Rationale weak or absent
- Some patients don’t respond, or respond badly
- Significant side effects
- Low compliance
Data Collection & Processing

Donor DNA Databank

1. What is your age group?
   - 17-20
   - 21-25
   - 26-30
   - 31-35
   - 36-40
   - 41-45
   - 46-50
   - 51-55
   - 56-60
   - 61-65
   - 66+

2. What is your sex?
   - Male
   - Female

3. To which culture background do you belong?
   - White, Scottish
   - White, other British
   - Black, Caribbean
   - Other
   - Asian, Pakistan
   - Asian, Bangladeshi
   - Asian, Indian
   - Asian, Chinese
   - Asian, other
   - Black, African
   - Hispanic

4. Were your grandparents born in Scotland?
   - Yes
   - No
   - Don’t know

Thank you for completing the questionnaire and agreeing to allow your blood to be used in the Generation Scotland ECO Study.

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SNBTS staff invite participation
Volunteer receives information about Study & Discusses it
Participant completes Consent Form & CMIR form
Blood Taken, Visible Marker attached to Filler
Blood & Filters Transferred to SNBTS Pet lab, tested
SNBTS barcode attached to blood tube for plasma
SNBTS barcode added to printed forms in donor session
Completed forms posted to U. of Edinburgh
Study reference ID number assigned to samples
Study reference ID assigned to database checked & filed
Link to SNBTS barcode broken after 2nd days
CMIR forms scanned into Database
Measure DNA Quantity and Quality (QC)
DNA of Blood
Future Biochemical Data from plasma
Phenotype Dataset
Genotype Dataset
Analytical Middleware
Sample Management Analysis
Research Output
LIMS Dataset
Reports

University of Edinburgh research team
Design & Print CMIR Questionnaire Forms
Samples received & Packed up by WTCRF
By SNBTS
Study Blood & Filters Transferred to WTCRF
Study Bloods & Filters Transferred to WTCRF
Data Management

- Collect
- Transfer
- Store
- Process
- Link
- Distribute
LIMS Management

Multi-site Sample Booking → Sample Storage → DNA Extraction & QC

Governance, Audit & Control

Right to withdraw
Follow Up
Medical Records & Prescriptions Linked to GS: SFHS data through Community Health Index (CHI) unique patient identifier
Health + Gene Data

- Data integration, mining & analysis
- Statistical & epidemiological testing
- Insight
- Inference
- Hypothesis generating
- Hypothesis testing
What this will allow us to do

1. Identify genetic risk factors
2. Understand the origins of disease
3. Reclassify disease
4. Devise new approaches to treatment & prevention
5. Undertake better clinical trials
6. Pave the way to new medicines - faster, cheaper, better
7. Make better use of existing medicines
Who owns & controls the data?

- Personal
- Research
- Medical
- Non-medical
- Commercial
- QC & QA
- Security
- Governance
Consultation
- Publics
- Policy makers
- Researchers
- Charities
- Industry

Comparator research

Education programme for healthcare professionals

Open consent

Data security & confidentiality

Ownership of genetic data

Benefit sharing
Generation Scotland
Scottish Family Health Study

A family based, volunteer study of gene predictors of disease & well being
Last year the prime minister asked Richard Thomas, the information commissioner, and Mark Walport, director of the Wellcome Trust, to review all aspects of data sharing.

They reported in July: "One area of research raises a Catch 22 dilemma. Researchers may wish to approach individuals in order to gain their consent to participating in a particular piece of research, for example the trial of a new treatment for a particular disease. The issue is how to identify these people in the first place. The requirement for 'consent to gain consent', which is largely limited to medical research, is a problem that requires a solution."
“There is pressure from researchers and from the prime minister to beef up UK research. They think of it as boosting UK Research plc. They want a mechanism by which people's clinical records could be accessed for the purposes of inviting them to take part in research, which at the moment is not allowed.

I think that would be a backward step. It would be saying there is a public interest in research that is so great that it overrides consent and confidentiality. That is not a proposition that holds up.”

Harry Cayton, Chair-elect, National Information Governance Board for Health and Social Care
Personal Genomics

www.23andMe.com
- **Build online health profiles.** You can enter your health conditions, medications, allergies, and lab results into your Google Health profile and you can name the profile anything you want. You can even create multiple profiles for family members or others you care for.

- **Import medical records from hospitals and pharmacies.** Choose from a list of Google Health partners to see if your hospital or pharmacy can send copies of your medical records or prescriptions to your Google Health profile. This way, you can save an accurate history of your medical conditions, medications, and test results all in one place.

- **Learn about health issues and find helpful resources.** Review trusted information on diseases and conditions and learn about possible medication interactions and other topics to talk your doctors about.

- **Search for doctors and hospitals.** You can search for a doctor's name or location, find a doctor's website, get directions to a doctor's office, and save a doctor's information to your medical contacts list.

- **Connect to online health services.** Browse the online health services directory to find services that are integrated with Google Health that can help you better manage your health needs.
Google search algorithms improve by 2 weeks on US Centre for Disease Control predictions of flu epidemics