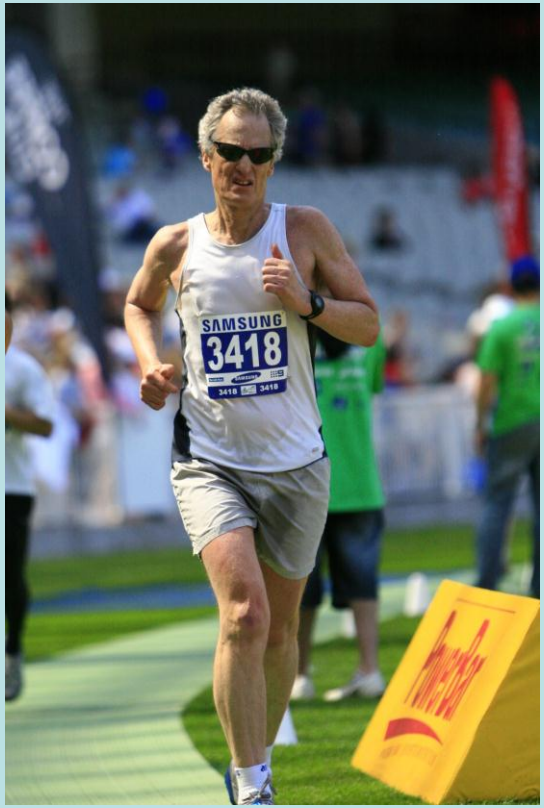
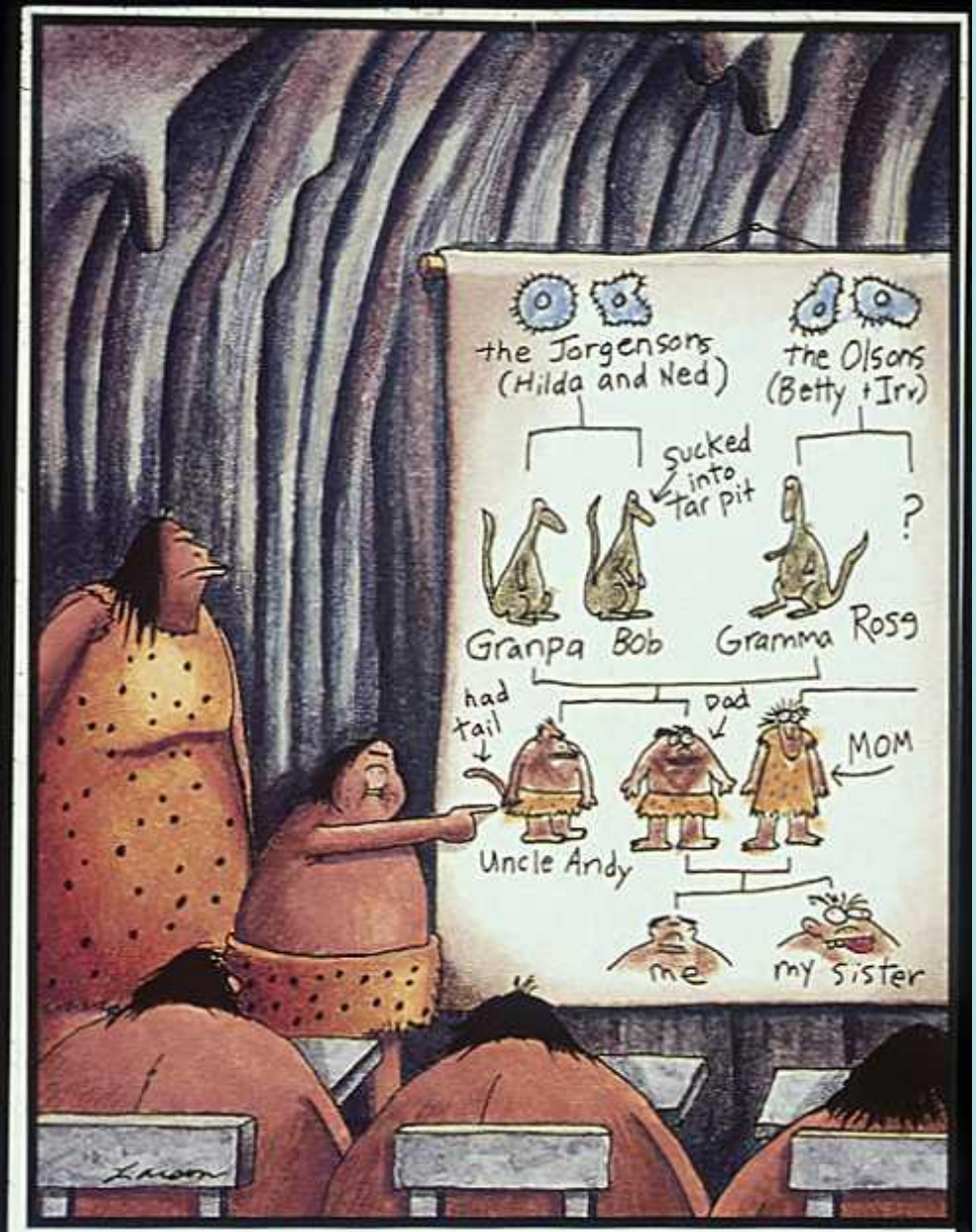
DUBLIN 2013



INCIDENTAL PITFALLS WITH WHOLE GENOME/EXOME SEQUENCING (WGS/WES) RESULTS

CLIN PROF JACK GOLDBLATT
DIRECTOR
GENETIC SERVICES AND
FAMILIAL CANCER PROGRAM WA



Dirk brings his family tree to class

FAMILY HISTORY ISSUES:

- Small family
- Adoption
- Secrecy
- Family dynamics
- Validation
- New mutation

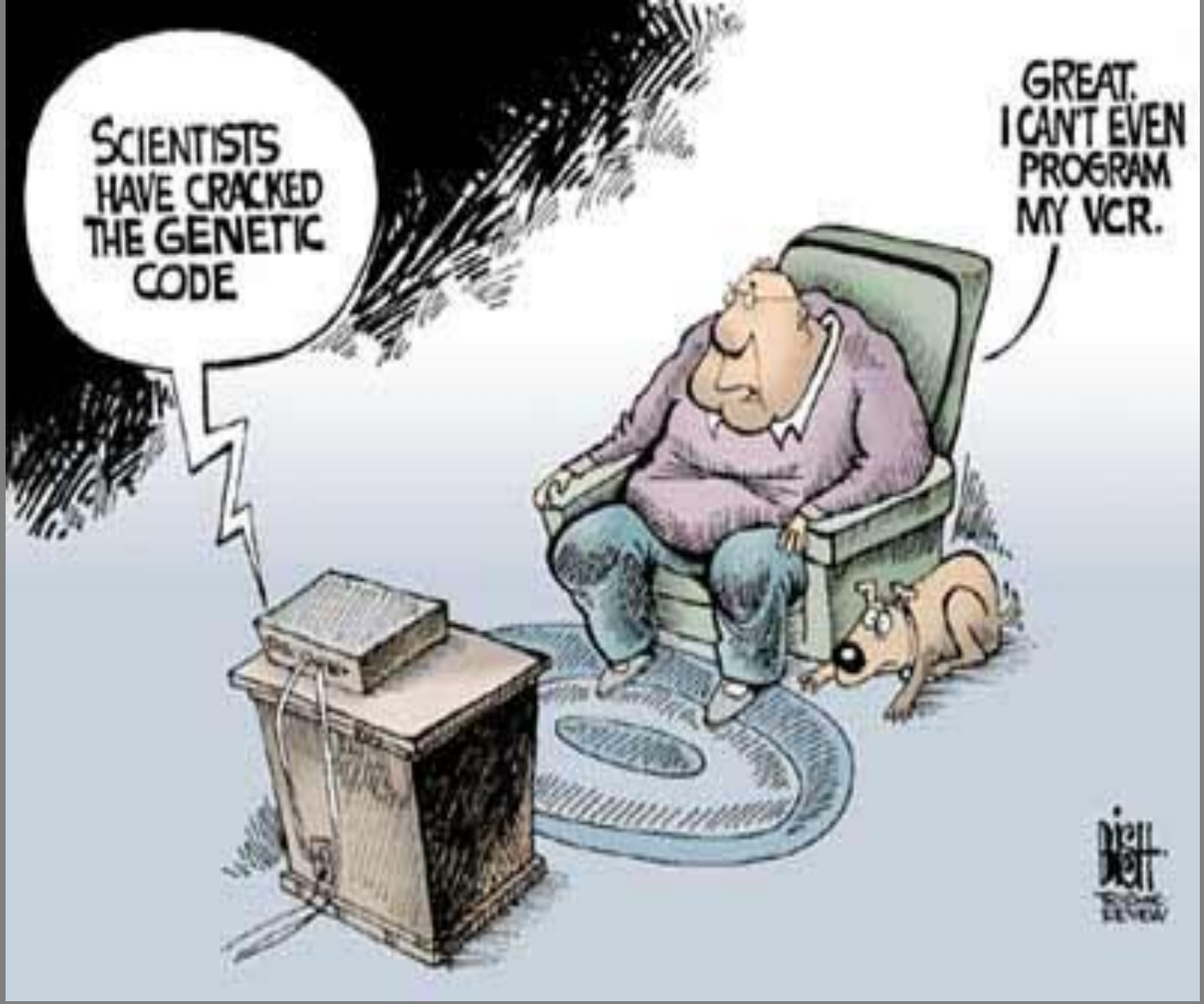
ADVANCES IN GENOMIC KNOWLEDGE THROUGH NEW TECHNOLOGIES

- 1977- Sequencing technologies-Sanger
- 1983 - PCR
- 2001- Human Genome Project-13 yrs, $2.7 billion, 1000s scientists
- 2005 - Massively parallel pyrosequencing platform → high throughput genomic sequencing, next generation sequencing, NGS.
- 2008 - Human genome sequenced in 5 months, $1.5million
- 2013 - <1 week, <$1000, 1 scientist

GENOMICS: IMPACT ON MEDICINE

- Diagnosis and disease susceptibility
  - Genetic Testing
- Genetic Counselling

  Reproductive options
- Disease Intervention
  - Genetic Therapy


SCIENTISTS HAVE CRACKED THE GENETIC CODE
GREAT. I CAN'T EVEN PROGRAM MY VCR.
Dilbert

DISCLOSURE OF GENETIC INFORMATION

Conflict between:-

- Individual autonomy and privacy (Patient in control)
- Preventing harm to others (Communitarian interest)

CRAIG VENTER WGS

- 4.1 million DNA variants, encompassing 12.3 Mb, of which 1,288,319 were novel, included > 3 million single nucleotide polymorphisms (SNPs),
- 53,823 block substitutions,
- 292,102 heterozygous insertion/deletion events,
- 559,473 homozygous indels, 90 inversions, as well as numerous segmental duplications and copy number variation regions.
- Non-SNP DNA variation accounts for 22% of all events identified, however they involve 74% of all variant bases

(Levy et al 2007)

“We are all at risk for something”

Francis Collins
M.D., Ph.D.,
Director, NHGRI

1000 GENOME PROJECT

“On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders”

1000 GENOME PROJECT-179 APPARENTLY HEALTHY INDIVIDUALS

- 281-515 missense substitutions predicted highly damaging
- 40-110 variants in HGMD as disease-causing mutations
- many polymorphisms putatively associated with disease

Xue et al. AJHG 2012, 91, 1022-1032 Dec 7.

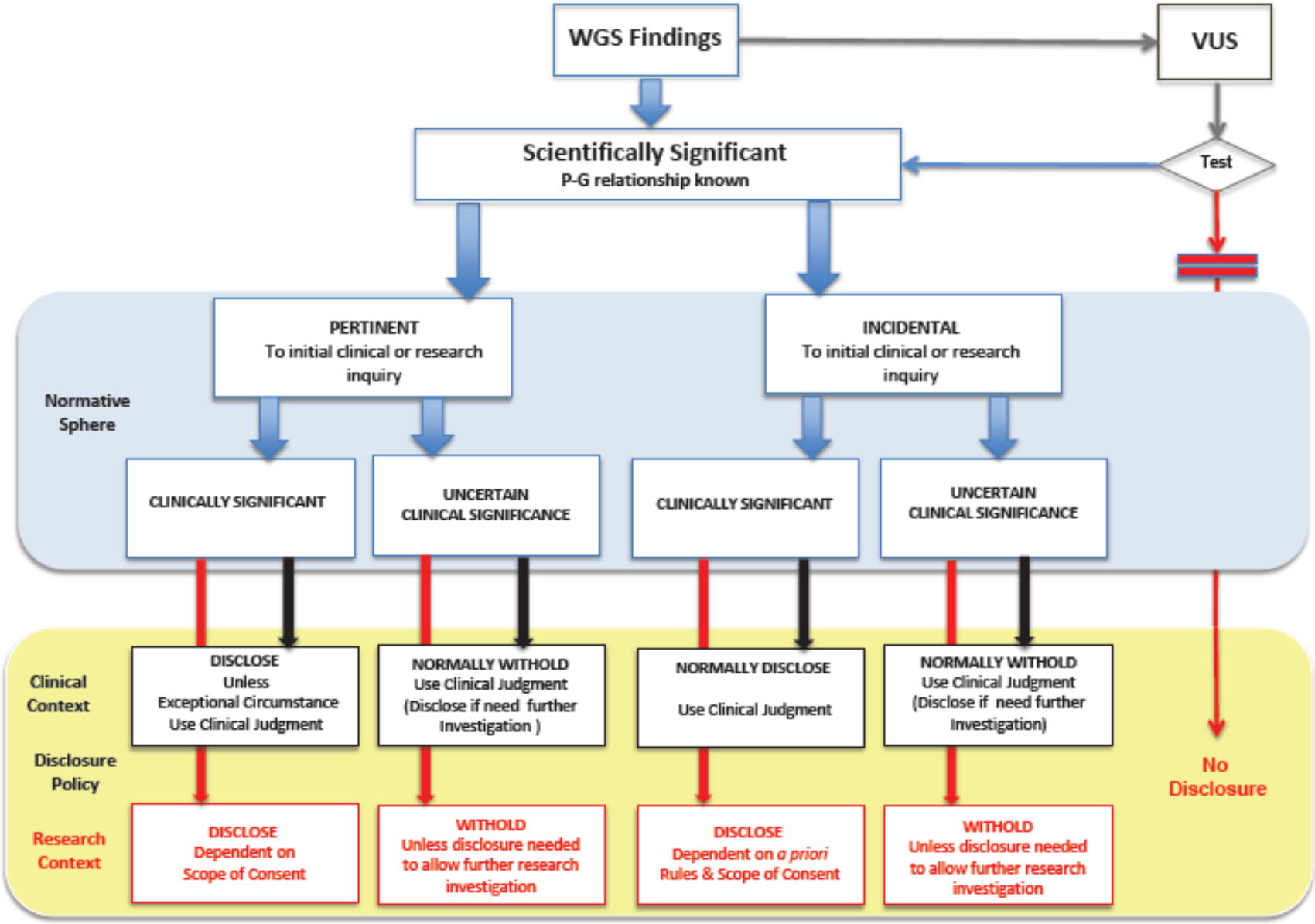
phgfoundation
making science work for health

Managing incidental and pertinent findings from WGS in the 100,000 Genome Project

A discussion paper from the PHG Foundation

April 2013

Figure 1


WGS Findings
VUS
Test
Scientifically Significant
P-G relationship known
Normative Sphere
PERTINENT
To initial clinical or research inquiry
INCIDENTAL
To initial clinical or research inquiry
CLINICALLY SIGNIFICANT
UNCERTAIN CLINICAL SIGNIFICANCE
CLINICALLY SIGNIFICANT
UNCERTAIN CLINICAL SIGNIFICANCE
Clinical Context
Disclosure Policy
Research Context
DISCLOSE
Unless Exceptional Circumstance
Use Clinical Judgment
NORMALLY WITHOLD
Use Clinical Judgment
(Disclose if need further Investigation)
NORMALLY DISCLOSE
Use Clinical Judgment
NORMALLY WITHOLD
Use Clinical Judgment
(Disclose if need further Investigation)
No Disclosure
DISCLOSE
Dependent on Scope of Consent
WITHOLD
Unless disclosure needed to allow further research investigation
DISCLOSE
Dependent on *a priori* Rules & Scope of Consent
WITHOLD
Unless disclosure needed to allow further research investigation

The Working Group acknowledged that its membership (and the *ad hoc* reviewers listed in the Appendix) were **not always in complete agreement**, **could not fully represent the opinions of others in the field**, and **did not have detailed knowledge of all of the conditions** that were considered.

Some have argued that incidental findings **should not be reported at all in clinical sequencing until there is strong evidence of benefit**, while others have **advocated that variations in any and all disease-associated genes could be medically useful and should be reported**. **The Working Group acknowledged that there was insufficient evidence about benefits, risks and costs of disclosing incidental findings to make evidence-based recommendations.**

We recognize that **there are insufficient data on clinical utility to fully support these recommendations** and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected.

American College of Medical Genetics and Genomics
ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

DISCLOSURES

LGB, JSB, WWG, CLM, AM, RLM, KEO, and HLR have grants related to genome sequencing.

LGB receives in kind research support from the Illumina Corp.

JSB and HLR are uncompensated members of Advisory Board members for Complete Genomics.

BRK, HLR, and MSWi are involved with clinical laboratories offering genome sequencing services.

AM, RLN, and JMO own stock in genome sequencing companies.

RLN provides compensated consulting to Complete Genomics.

JOD was employed by Illumina Corp. during the development of these recommendations

ACMG acknowledges in a document outlining its recommendations that it sought to reach a **compromise** between **"genetic libertarians who feel that patients have the right to full and complete accounting of all possible risks,” and "genetic empiricists who believe that there is insufficient evidence about the penetrance of most pathogenic variants in the general population to warrant the sharing of any incidental findings."**

Respect for persons – the duty to respect the autonomy of research participants and protect those with reduced capacity. **Respecting autonomy entails the provision of sufficient information to research participants so as to obtain their free, informed, and ongoing consent.**

Beneficence – the duty to maximize net benefits for research participants and for society as a whole, while advancing knowledge.

Non-maleficence – the duty to minimize and prevent harm to research participants.

Reciprocity – the duty to promote trust between researchers and research participants.

Population studies: return of research results and incidental findings Policy Statement
Bartha Maria Knoppers, Myle`ne Deschеˆnes, Ma'n H Zawati and Anne Marie Tasse´

The Public Population Project in Genomics and Society (P3G) is a not-for profit international consortium with members from more than 40 countries. Its objective is to lead, catalyze, and co-ordinate international efforts and expertise in order to optimize the use of population studies, biobanks, research databases, and other similar health and social science research infrastructures.

EJHG 2013, 21, 245-7

1. the participant has consented thereto in the initial consent form or at a later time;

2. the findings are analytically valid (ie, confirmed independently);

3. they reveal a significant risk of a serious health condition; and,

4. **they are actionable**.

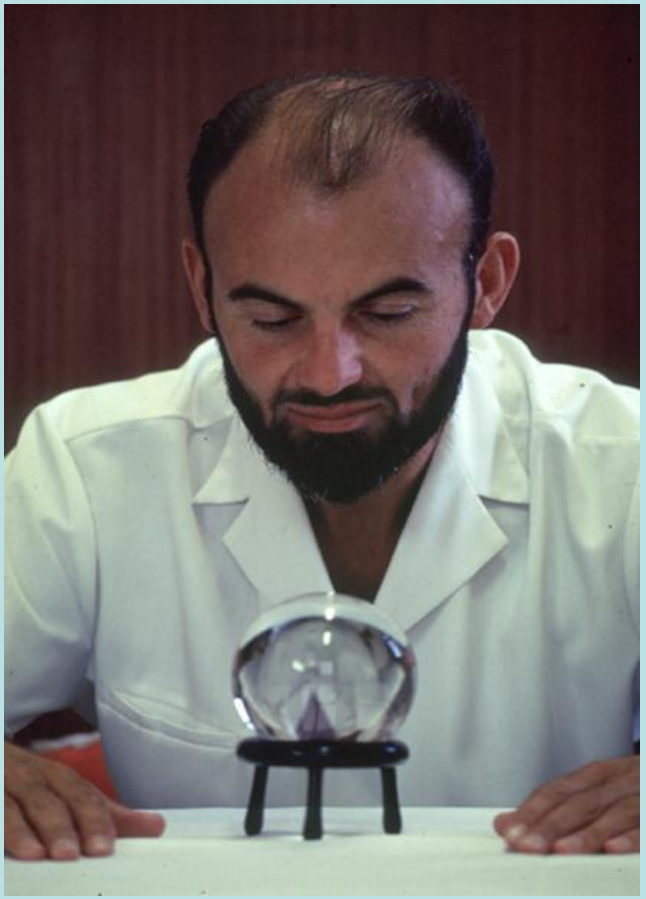
1. the participant has consented thereto in the initial consent form or at a later time;

2. the findings are analytically valid (ie, confirmed independently);

3. they reveal an established risk of likely health importance to the participant; and

4. **they have a likely therapeutic benefit.**

“To know is to predict, and to predict is to control”



August Conti,

19th century father of sociology.

- **Limited ability to tailor lifestyle and medical interventions responsibly and effectively to individual genomic profiles.**

- **Generate undue stress and the ‘worried well’ in individuals who over-interpret**

WHAT IS SO SPECIAL ABOUT GENETIC TESTING ?

- Complex information
- Interpretation
- Information on future health
- Family implications
- Equivocal clinical utility

PREDICTIVE TESTING ADULT-ONSET DISORDERS

- PSYCHOSOCIAL COPING
- FAMILY DYNAMICS
- INSURANCE
- EMPLOYMENT

GENETIC TEST EVALUATION

- Analytical validity
- Clinical validity
- Clinical utility
- Ethical, legal and social implications

INTERPRETATION OF WHOLE GENOME SEQUENCE

- Will detect many unusual or previously unknown genomic variants of uncertain clinical importance → unnecessary investigations → physical and psychological costs of increased testing

- ? What information will be fed back on estimated at least 100 variants ascertained

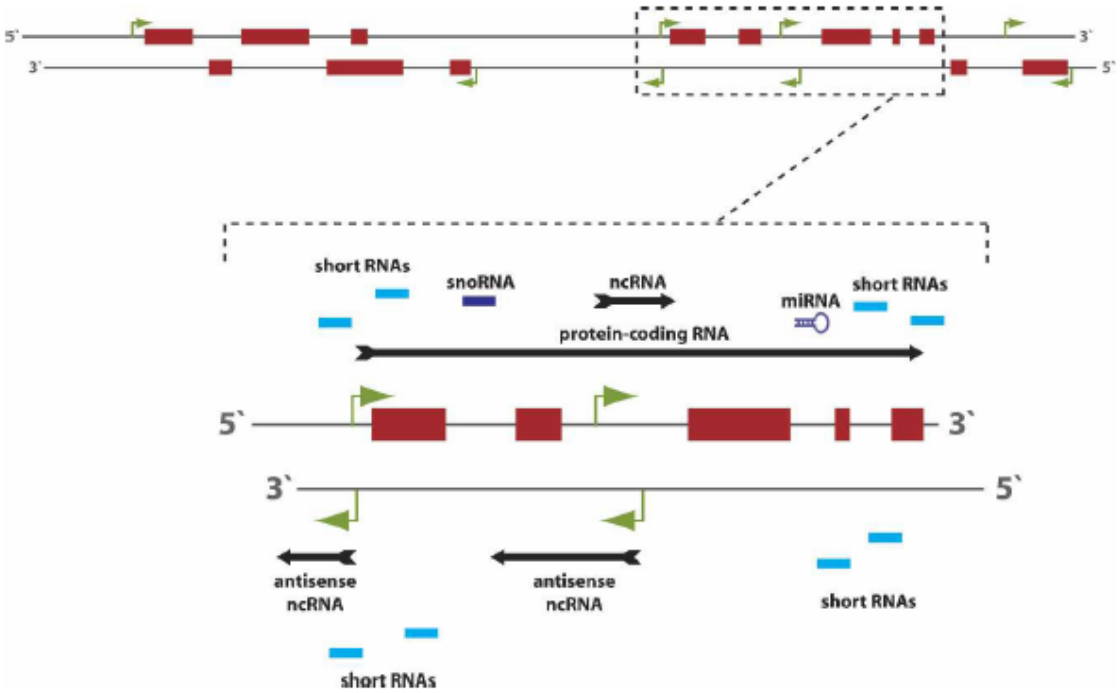


Figure 2. Transcriptional complexity of a gene. Hypothetical gene cluster with detailed zoom-in for highlighted gene demonstrates that a single gene can have multiple transcriptional start sites (TSSs) as well as many interleaved coding and noncoding transcripts. Exons are shown as red boxes and TSSs are green right-angled arrows. Known short RNAs such as snoRNAs and miRNAs can be processed from intronic sequences and novel species of short RNAs that cluster around the beginning and ends of genes have recently been discovered (see text).

Long QT Syndrome (SCN5A Gene) Mutation Analysis

Result: Variant likely to be pathogenic

Pathogenic Mutation: None

Unclassified Variants: c.[236C>G];[=] or p.[Pro79Arg];[=]

Comment:

Genomic sequencing of the SCN5A gene has identified the p.[Pro79Arg] variant in [redacted]. This change has not previously been published, however, in silico studies predict the variant to affect protein function. Family studies are available.

INTERPRETATION OF WHOLE GENOME SEQUENCE

- ? Good information on all known genetic disease and pharmacological risk
- Information difficult to obtain and keep up to date
- No centrally maintained repository of all rare and disease associated variants

VARIANTS IDENTIFIED WITH WGS/WES

- Penetrance or physiological effects dependant on:

  environmental factors

  modifier genes/epigenome

•Inadequate regulatory oversight.

•Scientific evidence for most associations between genetic variants and disease risk is insufficient to support useful applications.

•Vast majority of genetic variants are of extremely low predictive value.

•Limited ability to tailor lifestyle and medical interventions responsibly and effectively to individual genomic profiles.

•Generate undue stress and the ‘worried well’ in individuals who over-interpret.

•Overestimate the value of gene variants that lower disease susceptibility (‘protective’ variants), potentially leading to reduction in healthy, preventative behaviours.

Name: Susan S Age: 32 years Sex: Female Ancestry: Chinese.

Breast Cancer Risk: 10% Lifetime risk.

Your test results: rs2981582: CC, rs3803662: TT, rs889312: AC, rs3817198: CT rs13281615: AA

Breast cancer is one of the most common cancers affecting women. Breast cancer develops as a result of a combination of genetic and environmental risk factors. Knowing your risk of breast cancer can help your doctor develop a personalised management plan for you to prevent disease.

Average woman: 8% **You**: 10%

Your genetic make-up tells us that you are **1.25 times more likely** to develop breast cancer than the average woman

• The 10 SNPs analyzed by Wacholder et al. occur frequently in women, but each confers only slightly elevated risks of breast cancer (with odds ratios of 1.05 to 1.25).

• For women seeking advice on their personal risk of breast cancer, it is obviously too early to incorporate SNP testing into a counseling procedure, although such tests are already advertised for this purpose on the Internet.

A Tiny Step Closer to Personalized Risk Prediction for Breast Cancer. Peter Devilee and Matti A. Rookus. N Engl J Med 2010;362:1043-1045

Wacholder S, Hartge P, Prentice R, et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med 2010;362:986-93

FEEDBACK OF RESEARCH WES/WGS INFORMATION

- Individual results vs Publication/Newsletter
- Serious treatable/preventable -?moral obligation
- Other? eg uncertain significance, *less* severe, untreatable-potential benefits vs right to know
- Informed consent- eg adult onset disorders, behavioural/psychiatric predispositions
- ? A priori categorical framework-predetermined clinically relevant “bins”
- Findings that have a personal or legal significance such as ancestry, misattributed parentage, or consanguinity

GENETIC COUNSELLING FOLLOWING NGS

- Background research to assess implications of variants
- Direct patient contact
- Follow-up investigations and counselling on results

BARRIERS TO WGS/WES IN CLINICAL PRACTICE

- Concerns re genetic determinism/exceptionalism
- Translation gap and lack of evidence of clinical validity/utility
- Lack of genetics expertise amongst GPs and medical specialists
- Uncertainty about incidental findings and cost of following up
- ‘Medicalisation’ of the genome
- Fear of genetic discrimination and loss of privacy

PRACTICAL CONSIDERATIONS WITH WGS/WES IN CLINICAL PRACTICE

- Pre-test counselling on scope/implications
- Technical limits of sequencing method
- Accessible, well curated, genotype-phenotype data
- Uncertainty with some results (VUS) and require family studies
- Post-test counselling/educational resources
- Process for update communication to patient

•“A labelling effect may also occur, leading healthy patients to view themselves (or their children) as impaired based on abnormal test findings”.

•“As Cassel and Brennan have argued, physicians’ professional obligations include providing leadership to reduce the waste of health care resources; this role must include efforts to limit the unnecessary use of those resources that could flow from the marketing of genomic profiling to consumers.”

•Amy L. McGuire; Wylie Burke, JAMA, December 10, 2008—Vol 300, No. 22

WHOLE GENOME SEQUENCING IN MEDICAL PRACTICE

- Valuable but implementation challenging
- Mismatch between ability to interrogate human genome and ability to use that information to improve health
- Information is good and more better, however, ? counterproductive
- ? Maximum benefits and minimum harm
- **TARGETED** approach preferable
- Agreed **CONTRACT** pre-testing with patient

QUESTIONS FOR FUTURE RESEARCH ON WGS/WES

- What is the analytical validity, clinical validity, and clinic usefulness of personal genomic testing ?
- In what situation (medical, subset of patients, ancestry, environment, etc) would genotyping improve risk prediction and help target interventions ?
- What information does a consumer need to make an informed decision about personal genomic testing ?
- What information do healthcare providers need to educate patients about the value of personal genomic testing results ?
- What are the healthcare information technology needs and standards for storing and accessing genomic data in a confidential manner ?
- What is the role of government in determining policy on access to and regulation of genetic and genomic testing ?

CHEST X-RAYS AND NGS

- Poor example as diagnostic test only looking at the involved organ
- Compared to doing whole body imaging in coughing patient

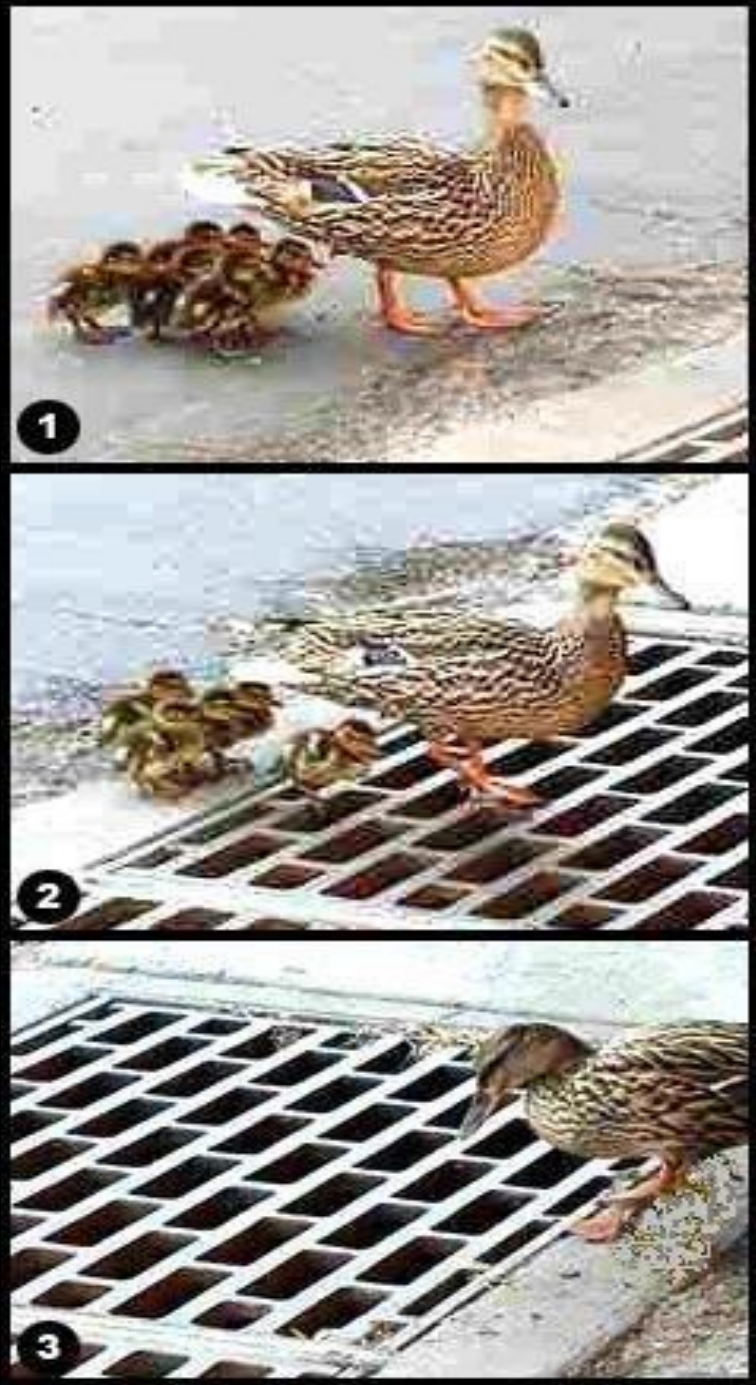
TIME

AUSTRALIA

Infidelity

It may be in our genes

Bad Parenting




WHAT'S COOKIN', WITCH?
WELL, I'M DABBLING IN A LITTLE GENETIC ENGINEERING.
NO KIDDIN'.
I'M GOING TO CROSS A HAWK WITH A DOVE...
WHAT'RE YOU TRYING TO GET?
A COHERENT FOREIGN POLICY...

END OF PRESENTATION

All images and information Jack Goldblatt 2013.

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