Enhancing the regulation of genetic tests using responsive regulation – an international analysis

Presentation to SACGHS, November 2007

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Outline

Scientific progress

- common disease markers – many discovered
  - Large numbers of markers, Modest effect sizes, many cherished markers failed to replicate

Clinical applications

- genetic risk assessment
- Pharmacogenetics

Policy problems

- Need for systematic, pre-market evaluation of new tests – but regulatory gaps – an international problem

Policy proposals

- Clarifying the role of IVD device regulations
- Modest proposals for improvements

Our research

Policy issues in the evaluation of genetic tests

How do we ensure that doctors, patients and healthcare systems can make informed decisions about the use of new genetic tests?

- **evidence generation** – the incentives and infrastructure required to generate a robust evidence base for new tests
- **evidence evaluation** – the regulatory mechanisms for independent evaluation of the evidence for new tests
- **evidence sharing** – the systems for ensuring that doctors, patients, healthcare policymakers and reimbursers have access to accurate and comprehensive information presented in a way that can be easily understood.

Methods

- Interviews and workshops with 80 individuals from key stakeholder groups – Europe and US (and Canada & Australia)

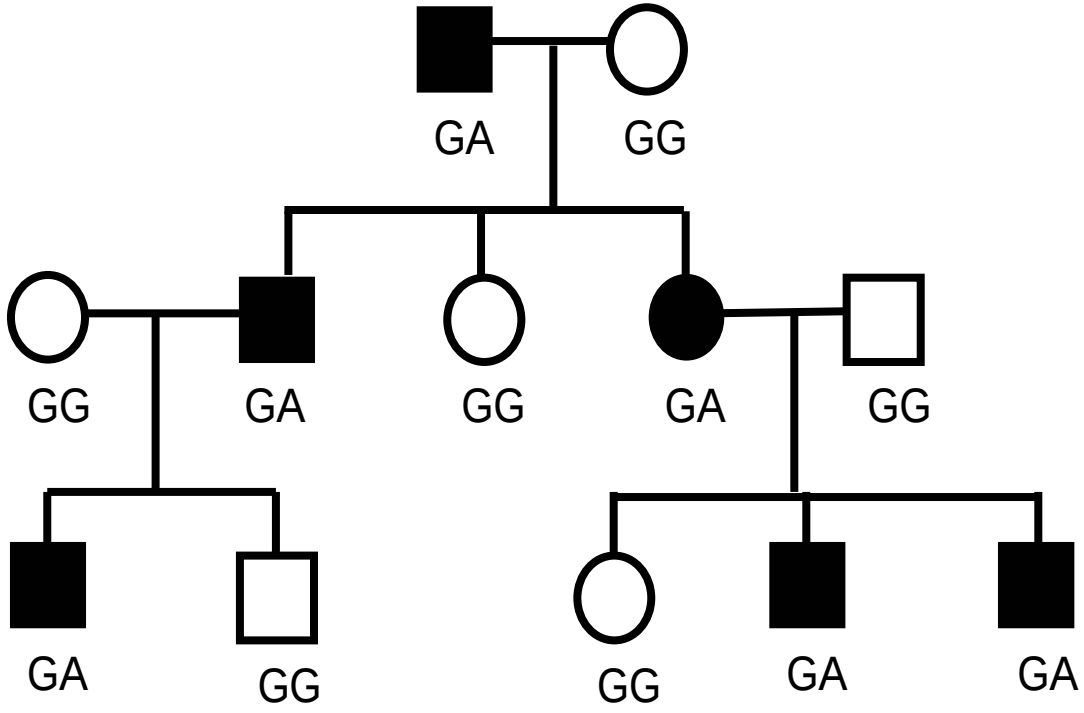
Conflicts of interest

- Wellcome Trust - independent research philanthropy
- Research project has been totally independent
- No commercial conflicts of interest
  (NIH and UK research grants)

Single gene disorders

DNA change determines disease: 100s of new tests

e.g. autosomal dominant disease



Common, complex diseases

Many SNPs, changes have *predisposing* effects

Gene variant more frequently in cases

Cases

Variant frequency: 33 %

Controls

Variant frequency: 16%

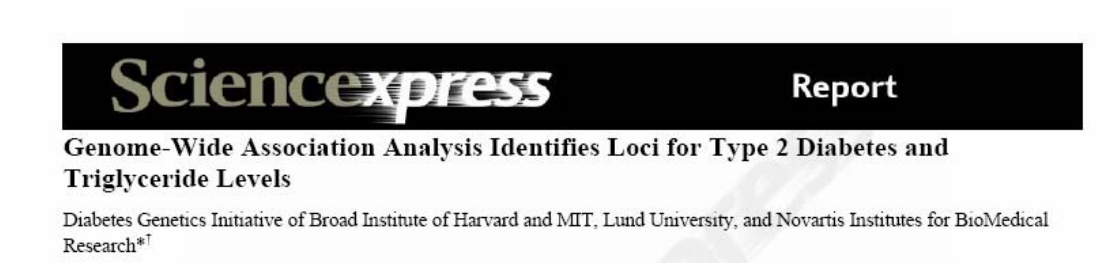
Some replicated Genome-wide association study results

GWA studies	**disease**	**gene**
The Wellcome Trust Case Control Consortium [1] & follow-up papers (eg Todd, Zeggini below)	bipolar disorder, coronary artery disease, Crohn's disease, rheumatoid arthritis, type1 diabetes and type 2 diabetes	24 independent associated signals
Klein [2]	Age-related macular degeneration	complement factor H (CFH)
Grupe [3]	Alzheimer's Disease	16 markers including APOE related
Coon [4]	Alzheimer's Disease	APOE
Moffat [5]	Asthma	ORMDL3
Gudbjartsson [6]	Atrial fibrillation	4q25 (close to PITX2)
Easton [7]	Breast cancer	FGFR2, TNRC9, MAP3K1, LSP1, H19
Tomlinson [8]	Colorectal cancer	8q24.21 locus
Zanke[9]	Colorectal cancer	8q24 locus
McPherson [10]	Coronary heart disease	9p21 (close to CDKN2A & CDKN2B)
Samani [11]	Coronary heart disease	9p21.3, 6q25.1 (MTHFD1L), 2q36.3
Rioux [12]	Crohn's disease	ATG16L1, PHOX2B, NCF4 and a predicted gene on 16q24.1 (FAM92B) (plus replication of CARD15, IL23R associations)
International MS Genetics Consortium [13]	Multiple sclerosis	IL2r, IL7-alpha and ILA-DRA
Maraganore [14]	Parkinson's disease	SEMA5A, PARK11
Winkelman [15] *& Stefansson H, et al. (2007)*	Restless leg syndrome	MEIS1, BTBD9, locus between MAP2K5 and LBXCOR1
Graham [16]	Systemic lupus erythematosus	IRF5
Todd [17]	Type 1 diabetes	12q24, 12q13, 16q13 and 18q11
Zeggini [18]	Type 2 diabetes	CDAL1, CDKN2A/CDKN2B, IGF2BP2, HHEX/IDE and SLC30A8
Bach [19]	Gall stone disease	coding SNP rs11887534 (D19H) in ABCG8
Frayling[20] (Exeter)	Body Mass Index (obesity)	FTO
Weedon [21] (Exeter)	*Childhood height*	HMGA2 (large set of additional markers in press)

Genome-wide association studies

Discovering many new variants

e.g. type 2 diabetes



Sciencexpress Report

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

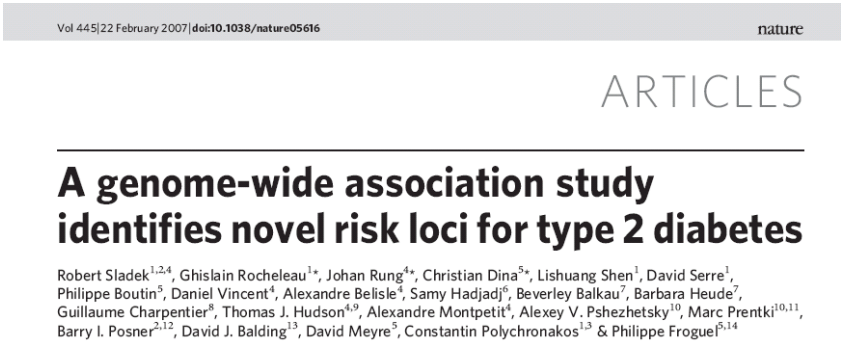
Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research*†

April 26th 2007

A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes

Valgerdur Steinthorsdottir[1,15], Gudmar Thorleifsson[1,15], Inga Reynisdottir[1], Rafn Benediktsson[2,3], Thorbjorg Jonsdottir[1], G Bragi Walters[1], Unnur Styrkarsdottir[1], Solveig Gretarsdottir[1], Valur Emilsson[1], Shyamali Ghosh[1], Adam Baker[1], Steinunn Snorradottir[1], Hjordis Bjarnason[1], Maggie C Y Ng[4], Torben Hansen[5], Yu Bagger[6], Robert L Wilensky[7], Muredach P Reilly[7], Adebowale Adeyemo[8], Yuanxiu Chen[8], Jie Zhou[8], Vilmundur Gudnason[3], Guanjie Chen[8], Hanxia Huang[8], Kerrie Lashley[8], Ayo Doumatey[8], Wing-Yee So[4], Ronald C Y Ma[4], Gitte Andersen[5], Knut Borch-Johnsen[5,9,10], Torben Jorgensen[10], Jana V van Vliet-Ostaptchouk[11], Marten H Hofker[11,12], Cisca Wijmenga[13,14], Claus Christiansen[6], Daniel J Rader[7], Charles Rotimi[8], Mark Gurney[1], Juliana C N Chan[4], Oluf Pedersen[5,9], Gunnar Sigurdsson[2,3], Jeffrey R Gulcher[1], Unnur Thorsteinsdottir[1], Augustine Kong[1] & Kari Stefansson[1]

April 26th 2007



Vol 445|22 February 2007|doi:10.1038/nature05616 nature

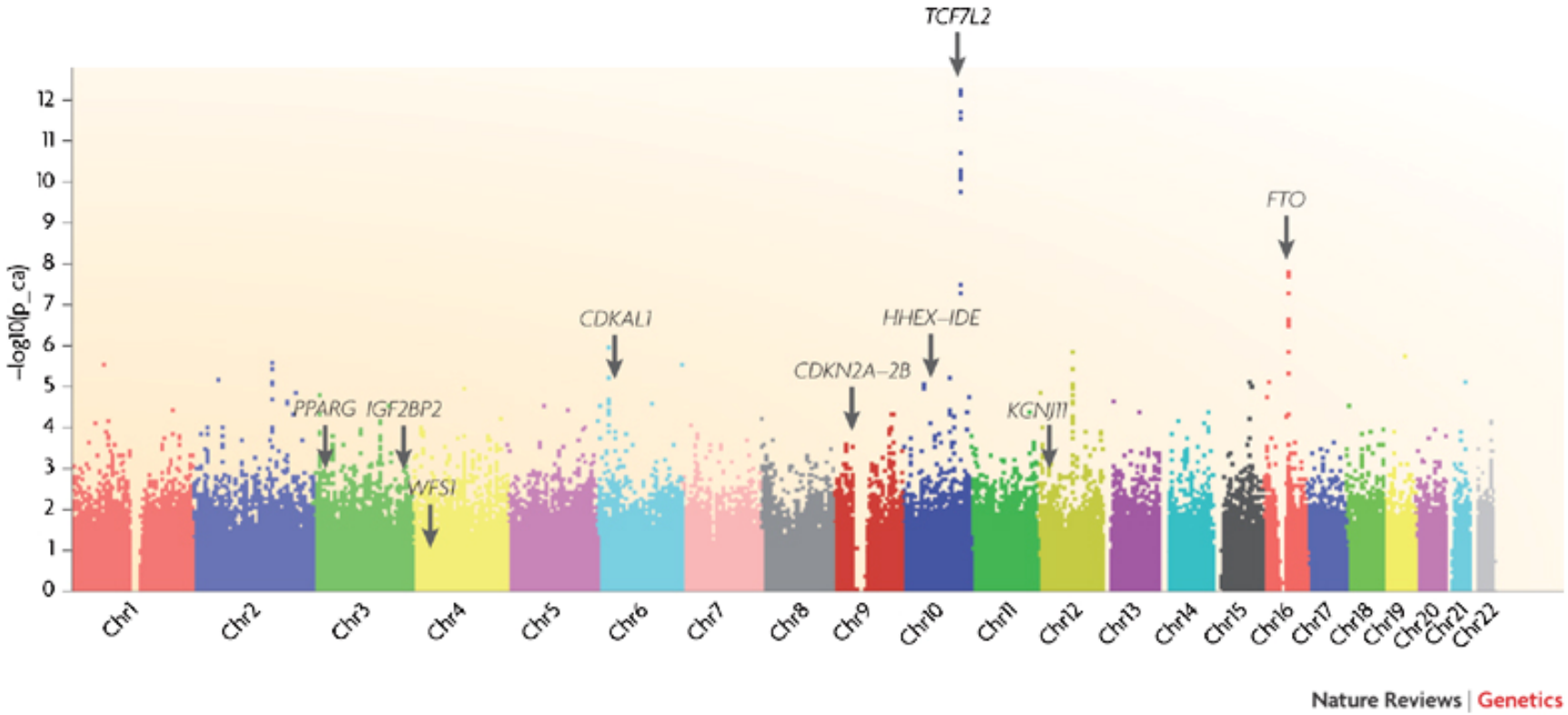
ARTICLES

A genome-wide association study identifies novel risk loci for type 2 diabetes

Robert Sladek[1,2,4], Ghislain Rocheleau[1*], Johan Rung[4*], Christian Dina[5*], Lishuang Shen[1], David Serre[1], Philippe Boutin[5], Daniel Vincent[4], Alexandre Belisle[4], Samy Hadjadj[6], Beverley Balkau[7], Barbara Heude[7], Guillaume Charpentier[8], Thomas J. Hudson[4,9], Alexandre Montpetit[4], Alexey V. Pshezhetsky[10], Marc Prentki[10,11], Barry I. Posner[2,12], David J. Balding[13], David Meyre[5], Constantin Polychronakos[1,3] & Philippe Froguel[5,14]

Genome wide study of Type 2 diabetes

WTCCC study – Oxford and Exeter

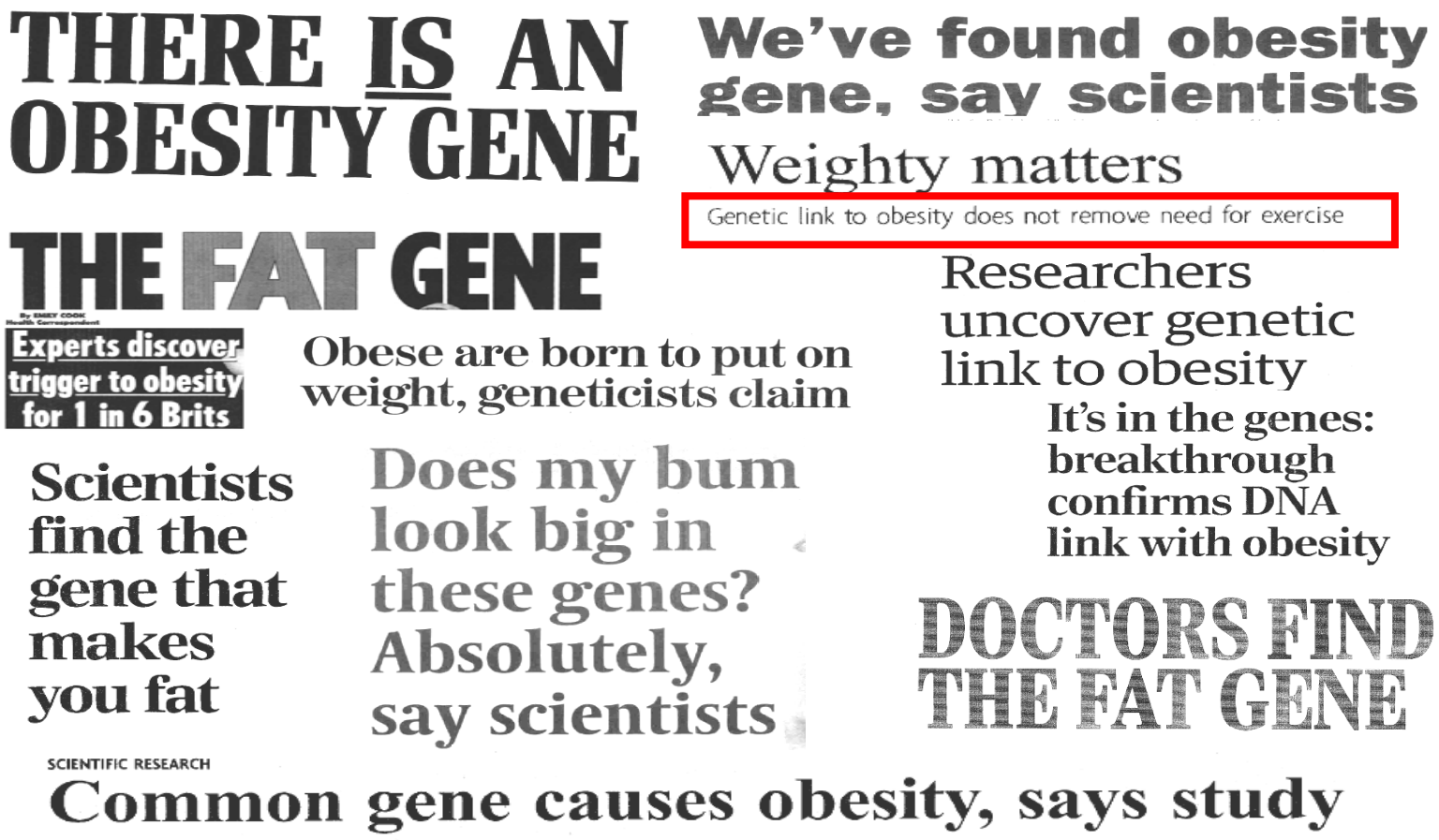


From Frayling, 2007

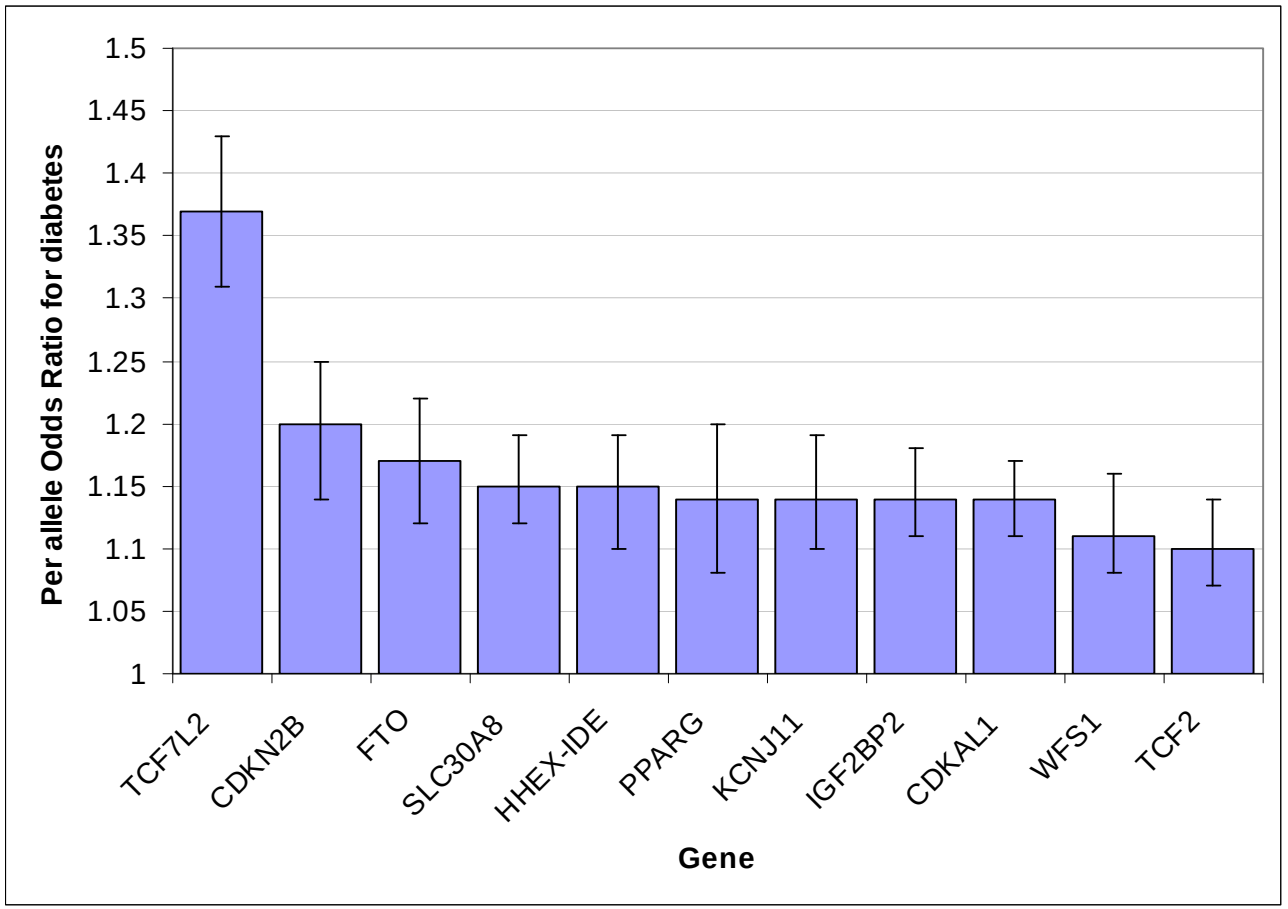
Misreporting of the science

FTO gene = 3Kg difference.

Presented in media as "THE fat gene"



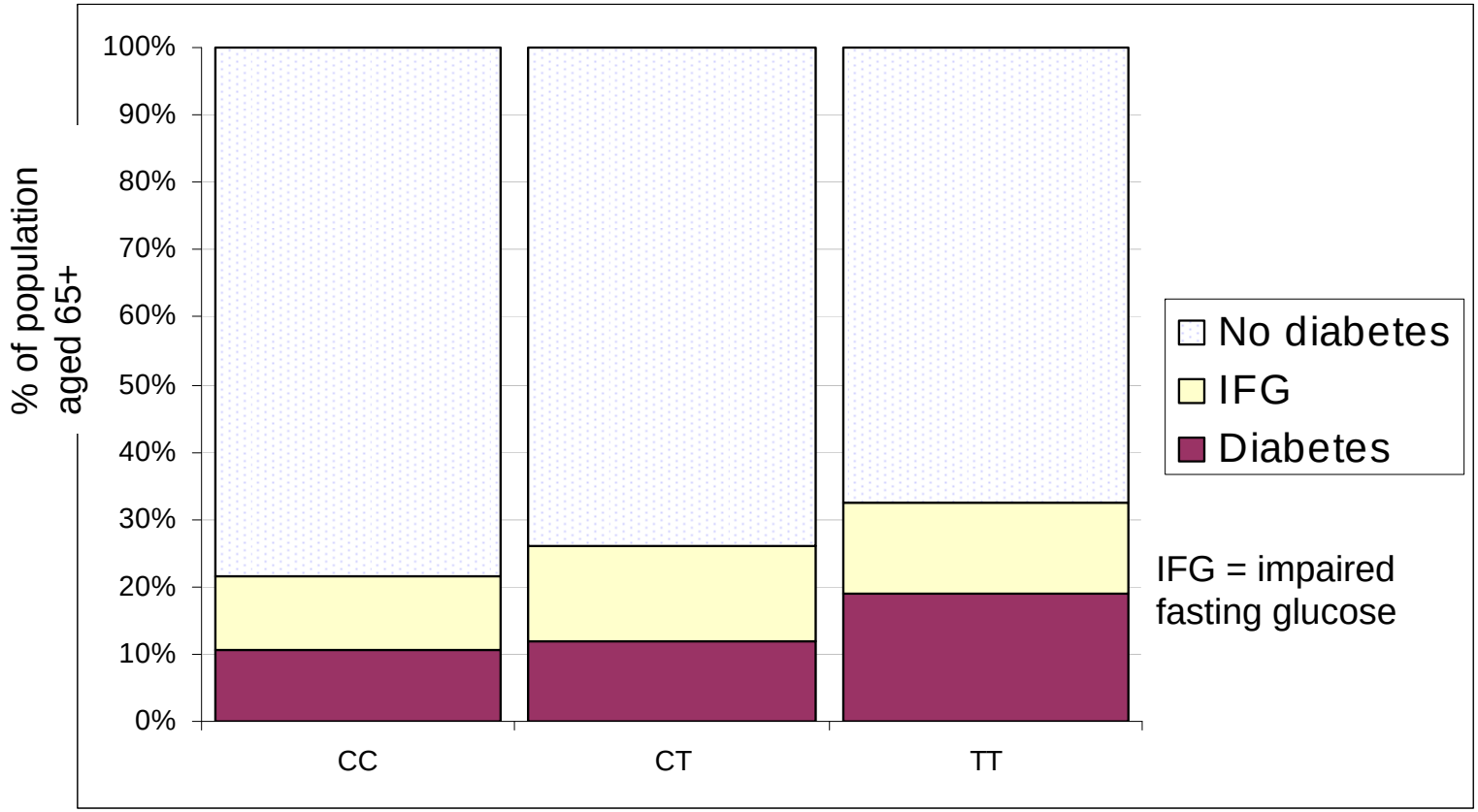
Type 2 Diabetes SNPs – lots of markers, modest effects



Predictive value alone

Biggest effect variant for diabetes Type 2 = TCF7L2

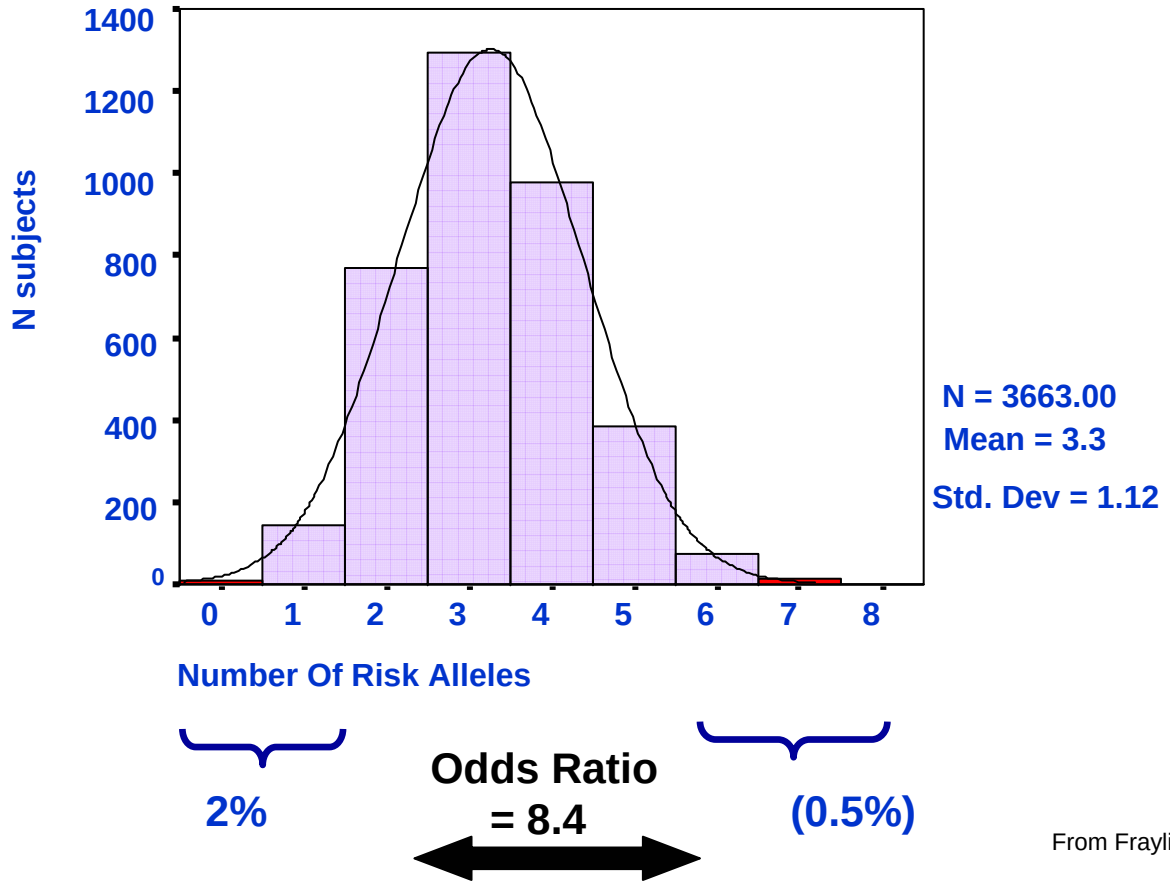
Test results in general population (InCHIANTI study, Italy, aged 65+)



Melzer D et al, BMC Med 2006 Dec;20;4(1):34.

Combining SNPs into Algorithms and formulae – the future norm

type 2 diabetes



From Frayling et al

Failure to replicate

GWAs for myocardial infarction

Not one of the previous markers were significant!

Morgan TM, et al. Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study.
JAMA 2007; 297(14):1551-1561.

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1]* Gudmar Thorleifsson,[1]* Andrei Manolescu,[1]* Solveig Gretarsdottir,[1] Thorarinn

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1]*† Alexander Pertsemlidis,[2]* Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A.

The future is now

- **InterGenetics launch OncoVue in Europe**

The future is now

- **deCODE launch T2, AF & MI in US**

deCODE diagnostics home | For physicians | About deCODE T2™ | About deCODE

About deCODE T2™
Understanding risk
Empowering prevention
About type 2 diabetes
Frequently Asked Questions

deCODE genetics

About deCODE T2™

deCODE genetics – a global leader in applying human genetics to create better healthcare – offers deCODE T2™, a DNA-based test designed to help individuals, working with their doctor, better understand their risk of type 2 diabetes (T2D) and to enable more effective prevention strategies.

Understanding risk can empower prevention. Many major lifestyle and environmental risk factors for type 2 diabetes are well known – obesity and its causes, including poor diet and lack of exercise - and it is well established that addressing these risk factors can reduce the risk of becoming diabetic. Inherited risk factors also influence individual susceptibility to T2D.

deCODE T2™ is a reference laboratory test to detect a version of a single SNP (single nucleotide

Type 2 diabetes is a

The future is now

- **DTC polygenic risk assessment in UK**

Where's the harm?

'THE TEST SHOCKED ME INTO EATING BETTER'

"I was worried about stroke as it runs in my family, but it seems my genes are okay for that. However, **I have a 140-fold increased risk of cancer as I don't clear pollutants very well** – I could lower this risk by eating more fruit and vegetables, particularly cruciferous ones like broccoli and cabbage."

Victoria Hanlon, 27 year-old account executive
after taking Genetic Health's 'Premium' test
***Grazia*, 26 March 2007**

Where’s the harm?

‘UNSUBSTANTIATED AND OVERBLOWN CLAIMS’

“If Virginia Ironside thinks a genetic test can accurately predict her risk of cancer, heart disease or Alzheimer's, she is sadly mistaken. Genetic tests, such as the one she had, are **more or less useless** in predicting an individual's risk of developing these diseases. The companies that sell these tests are making **unsubstantiated and overblown claims** about the predictive power of these tests.“

Rob Elles, Chair of British Society of Human Genetics, *et al*
***The Independent*, November 2007**

Slow down, you move too fast

"[There has been] a noticeable lack of consensus within the genetics community about exactly when a test for a new marker was sufficiently validated for it to enter into clinical service.

Some labs rushed to provide testing after the first publication, while others waited until the result had been replicated in multiple studies or multiple ethnic groups."

Emily Winn-Deen, Cepheid

(ex-SACGHS member)

***IVD Technology* December 2003**

Major policy reports

US

- **1975 – *Genetics screening programmes, principles and research* (National Academy of Sciences)**
- **1994 - *Assessing genetic risks* (Institute of Medicine)**
- **1999 - *Promoting safe and effective genetic testing in the United States* (Task Force on Genetic Testing)**
- **2000 - *Enhancing the oversight of genetic tests: recommendations of the Secretary's Advisory Committee on Genetic Testing* (SACGT)**
- **2004 – *Reproductive genetic testing: issues and options for policymakers* (Genetics and Public Policy Center)**

UK

- **1994 - *Genetic screening – ethical issues* (Nuffield Council on Bioethics)**
- **2000 - *Genetics and health – policy issues for genetic science and their implications for health and health services* (Nuffield Trust)**
- **2000 - *NHS Laboratory services for genetics* (Report for the Department of Health)**
- **2003 - *Genes direct. Ensuring the effective oversight of genetic tests supplied directly to the public* (Human Genetics Commission)**

EU

- **2000 - *Report of European Parliament's Temporary Committee on Human Genetics and New technologies in modern medicine***
- **2003 - *Towards quality assurance and harmonisation of genetic testing services in the EU* (Institute for Prospective Technological Studies)**
- **2004 - *Ethical, legal and social aspects of genetic testing: research, development and clinical applications* (EC Expert Group)**

Other countries

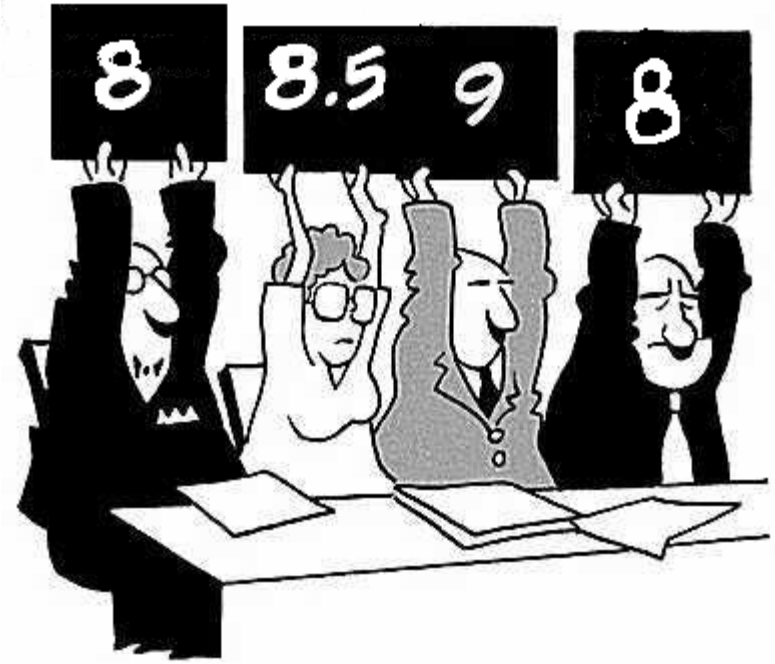
- **2002 - *ALRC 96 Essentially Yours: the protection of human genetic information in Australia* (Australia Law Reform Commission and Australian Health Ethics Committee)**
- **2001 - *Genetic services in Ontario: mapping the future* (Provincial Advisory Committee on New Predictive Technologies)**
- **2001 - *Genetic investigation of healthy subject – report on presymptomatic gene diagnosis* (Danish Council of Ethics)**

International

- **2001 - *Genetic testing: policy issues for the new millennium* (OECD)**
- **2005 - *Quality assurance and proficiency testing for molecular genetic testing: summary report of a survey of 18 OECD member countries* (OECD)**

A policy consensus

Genetic tests should not enter routine clinical practice without thorough independent evaluation



ACCE evaluation framework

Analytic validity – accuracy of test identifying the biomarker

Clinical validity – relationship between the biomarker and clinical status

Clinical utility – likelihood that test will lead to an improved outcome

ELSI

Mind the gaps

Regulatory gaps comparison

	Risk class	Scope of review	LDTs	General approach
USA	Moderate / high	Analytic and clinical validity	Only small subset	Proactive
Europe	Low	Only if clinical claims?	Yes, but some exemptions, (inc. overseas suppliers?)	Reactive
Canada	Moderate	Analytic and clinical validity	Authority not clear	
Australia	Moderate	Only if clinical claims?	Yes	

UK - developments

UK developments

- ACGT Code of Practice
- UK Genetic Testing Network – gene dossiers
- National Screening Committee reviews regulation of commercial screening services
- Human Genetics Commission renews its interest in regulation of DTC genetic tests

Europe - developments

European developments

- Creation of EuroGentest (QA / CRM)
- Revision of IVD Directive (imminent)
- EMEA work on PGx – FDA collaboration (VGDS)
- Participation in OECD QA guidelines for MGT
- Council of Europe - Protocol on Genetic Testing

Global - developments

Australia

- Complete revision of IVD regulations
- Guidance on nutrigenetic tests

Canada

- Guidance on PGx tests

International developments

- OECD QA guidelines for MGT
- GHTF activities
- ICH work on PGx
- HUGENet

IVDMIA guidance

An important step forward

- IVDMIA guidance correctly identifies area where FDA intervention most urgently needed
- Guidance has brought clarity to FDA's position
- Now FDA must consider its broader responsibilities regarding LDTs

What's missing?

IVDMIA guidance is not comprehensive

- Many monopolistic providers not covered e.g. Myriad
- Other homebrew tests where unlevel playing field remains e.g. Roche Amplichip - FDA-approved must compete with non-approved tests
- Other high-risk tests e.g. PGx and DTC

IVD sector innovation

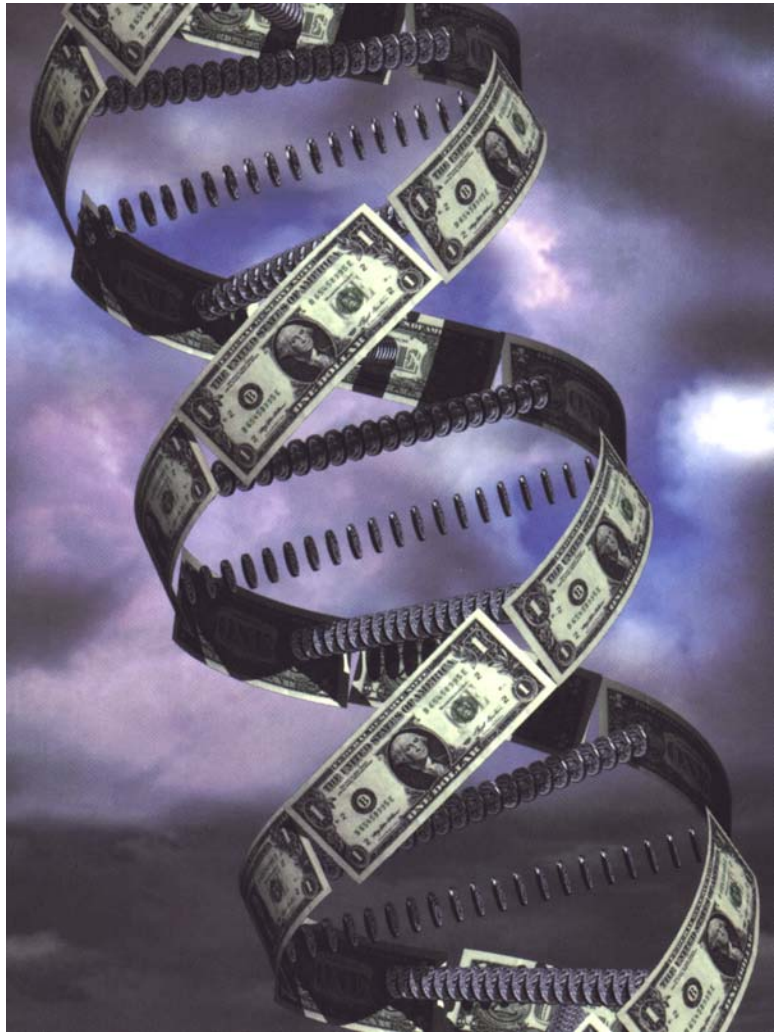
Traditional model

- IP in platforms
  - Me-too products within two years
  - Relatively low profit margins
  - Multiple players involved in innovation

IVD sector innovation

Molecular model

- Greater IP in biomarkers
  - Me-too products on market more slowly
  - Higher profit margins
  - Reference lab route
  - **Companies competing on quality of clinical data**



Regulating monopolies

Challenges

- No peer review in the field by lab directors;
- Clinical claims – a harder sell to recoup investment?

What should we do?

Six reasons to require premarket review for LDTs as medical devices

1) They can pose same risks as kits
2) LDTs are big business; leading companies are bigger than many kit manufacturers
3) Small labs do not get a CLIA exemption, why should they receive an FDA exemption?
4) It is possible to do it (e.g. NY State / MammaPrint)
5) This is clearly the international trend (Europe / Australia)
6) Reference lab monopoly issue

Policy in practice - problems

Implementation problems

- need to balance evaluation, innovation and access;
- lack of clarity on the respective roles of different gatekeepers;
- FDA resources;
- industry reluctance

Can we have our cake and eat it?

Policy in practice - problems

Implementation problems

- need to balance evaluation, innovation and access;
- lack of clarity on the respective roles of different gatekeepers;
- FDA resources;
- industry reluctance

Solutions

- focus pre-market review on truth-in-labelling;
- greater emphasis on postmarket controls and clarity role of gatekeepers

Responsive regulation

Enforcement pyramid

Braithwaite J et al The governance of health safety and quality. Canberra: Commonwealth of Australia, 2005.

Responsive regulation

One size does not fit all

Responsive regulation

Three core regulatory functions

- Information gathering
- Standard setting
- Enforcement

Role of IVD device regulations

What they can't do

- Deal with ethical/social issues such as genetic discrimination
- Regulate clinical practice issues such as informed consent and confidentiality of personal data
- Evaluate clinical utility - best left to HTA and clinical practice guidelines

Role of IVD device regulations

What they can do

- Premarket review of analytic and clinical validity
- Set clear evidence standards for market entry
- Monitor performance in postmarket environment
- **Ensure truth-in-labelling and truth-in-promotion**

Asymmetries of information

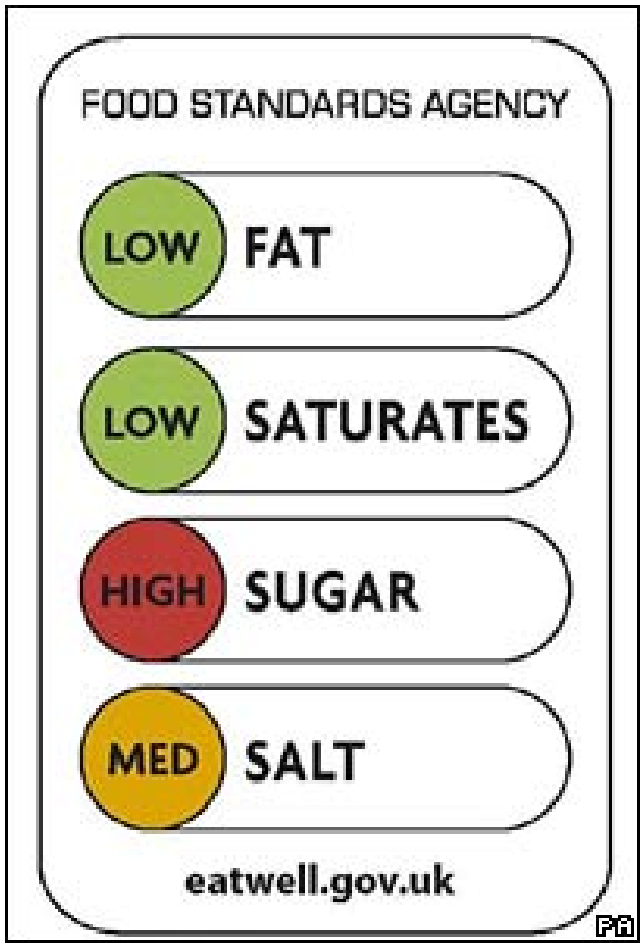
- **Can we level the playing field?**

Pre-market review

- **Regulation by information disclosure**
  - Truth-in-labelling (and truth-in-promotion)

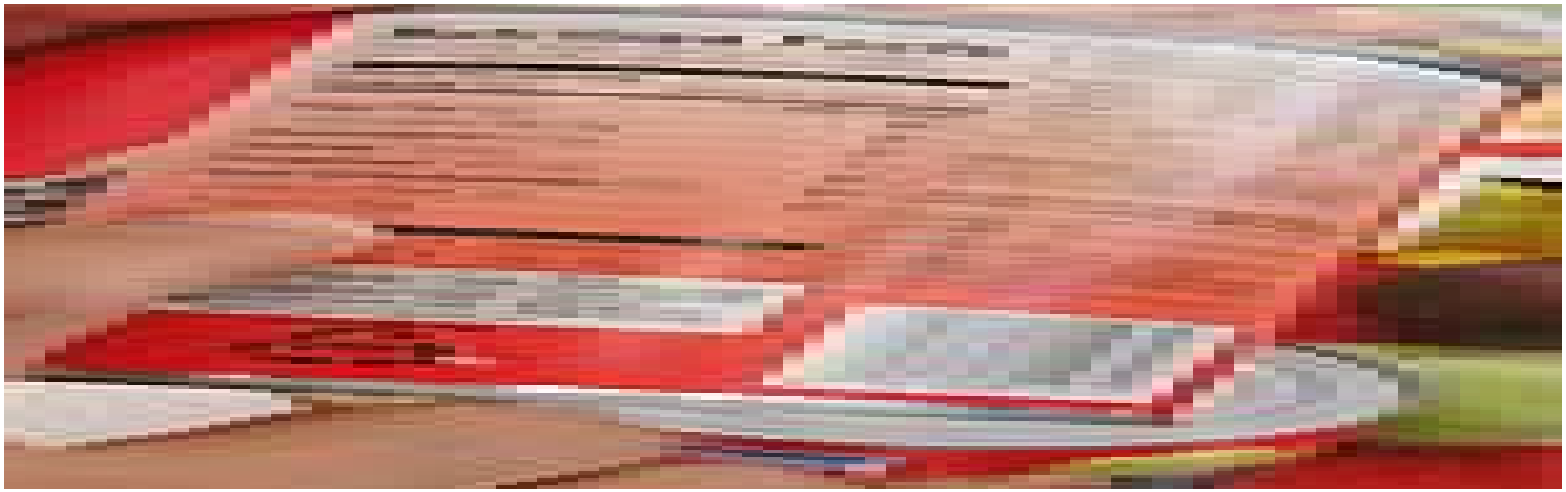
Pre-market review

- **Regulation by information disclosure**
  - Truth-in-labelling (and truth-in-promotion)
  - Data quality kitemarking



Pre-market review

- **Regulation by information disclosure**
  - Truth-in-labelling (and truth-in-promotion)
  - Data quality kitemarking
  - Expanding the definition of a label



Pre-market review

- **Regulation by information disclosure**
  - Truth-in-labelling (and truth-in-promotion)
  - Data quality kitemarking
  - Expanding the definition of a label
  - Encouraging transparency

Postmarket controls

- **Reimbursement**
  - *de facto* regulator?
  - HTA e.g. Amplichip
- **Clinical governance**
  - Increased use of and better funding for clinical guidelines
- **Independent sources of information**
  - LabTests Online, GeneTests, OrphaNet etc.

Alternatives

Enforcement pyramid

Braithwaite J et al The governance of health safety and quality. Canberra: Commonwealth of Australia, 2005.

FDA's potential for flexibility

"… PMA and 510(k) are our usual review processes - but we have on the table a wild and wide variety of abbreviated forms of those tools which allow us to do all kinds of things, including conform to standards or approach almost mechanisms of self-certification and to use smaller data sets and different data sets.

So we are in a position, frankly, to create tools that might fill the gap here that we probably would not have brought to the table four or five years ago."

Steve Gutman, transcript of meeting of

SACGT working group on test classification

Alternatives

Third party review and FDA as meta-regulator

- European model
- Australian model
- Role for NY State / CETT *and others*

Alternatives

Registry concept

- Publicly available register of
  - all labs
  - evidence dossiers for all tests
- Issues
  - Who can guarantee quality of information?
  - Who deals with complaints?

Summary

Key ideas

- pre-market review for truth-in-labelling
- conditional licensing
- enhance postmarket controls
- create more flexibility in role of FDA
- strengthen role of other gatekeepers

Research team

Stuart Hogarth, University of Nottingham

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