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Practical Challenges for Clinical Genetic Services

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and

Department of Genetic Medicine

CMFT

UK

Practical Challenges for Clinical Genetic Services

- Genetics in the clinic
  - What we do in Genetic Medicine that others don't
  - Incorporating research
  - Issues we have faced
- How Genetic Medicine is changing
  - Array technologies
  - Pharmacogenetics
  - Treatment of genetic disease
  - Next generation sequencing
  - Concerns about DTC testing

Medical Genetics as a clinical specialty
What we do in genetics that others don't

- Services for affected patients and families
- All age groups
- All body systems
- Over generations
- Knowledge of rare disorders
- Screening, monitoring and anticipating complications
- Genetic counselling to affected and apparently healthy people
- Major source of information
- Education role

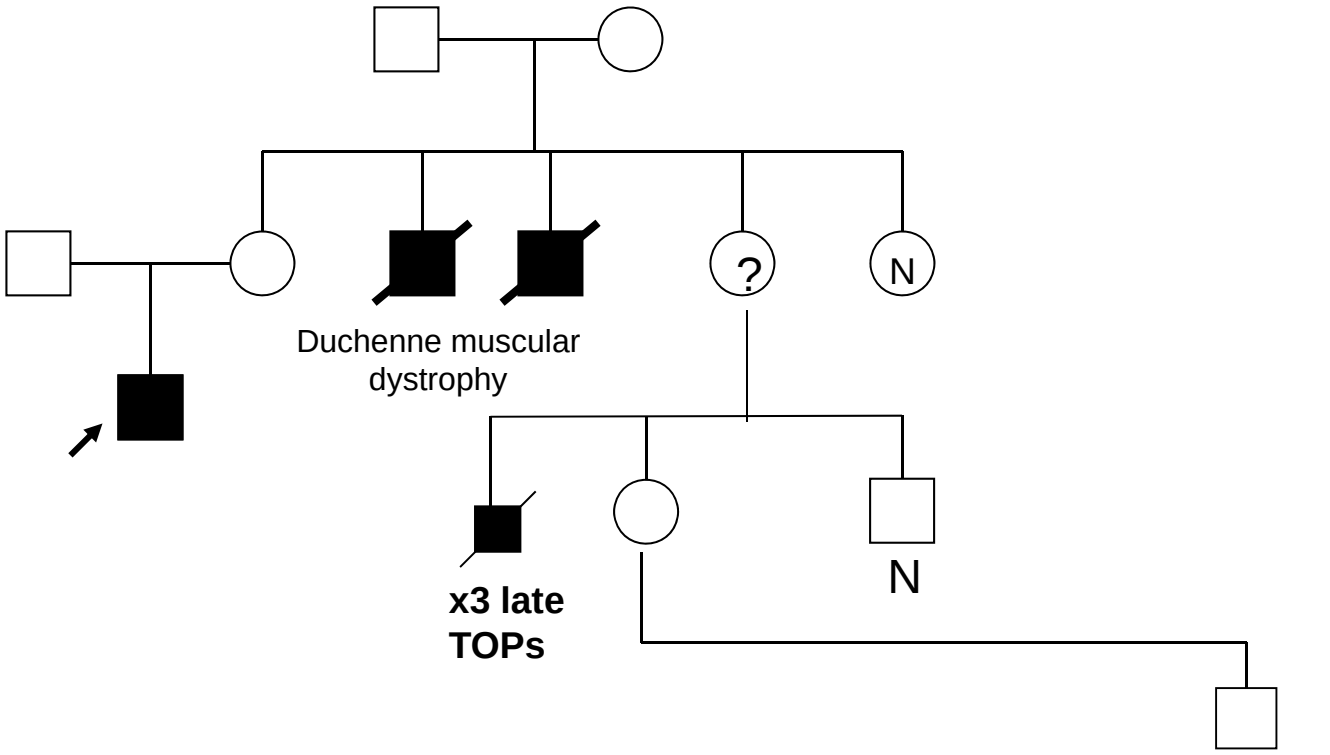
Practical Challenges for Clinical Genetic Services

- Recognition of clinical/medical genetics as a medical specialty
- Recruiting the right people with the right background
- Ensuring the curriculum reflects the changing nature of the specialty

Genetics Medicine has always incorporated research

- Genes mutated in almost all ‘common’ monogenic disorders found
  - Translated into services for patients
    - Diagnostics, risk assessment, anticipatory care
- Genetic clinics were never limited to families with chromosomal and single gene disorders
- Complex cohorts collected
  - cancer, clefting, obesity, diabetes, learning disability, dementia etc
  - *pedigrees and phenotypes well documented*

Genetics involves whole families and information changes over time

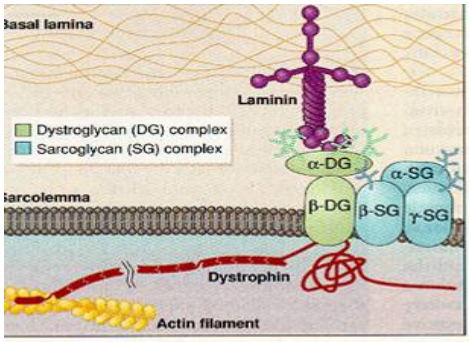


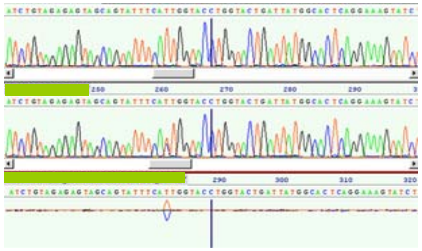
Genetic tests can make a difference

DMD

DNA tests - effect on numbers at risk

1987 214 families, 929 females at risk





2009 320 families, 308 females carriers

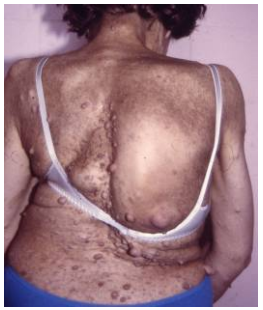
NWR Genetic Family Register

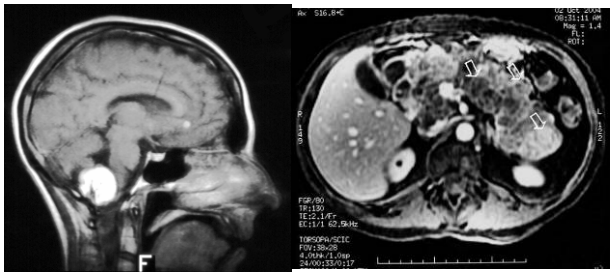
Practical challenges for clinical genetic services

the rise of cancer genetics – now 50% of referrals

Monogenic cancer prone syndromes

NF





VHL

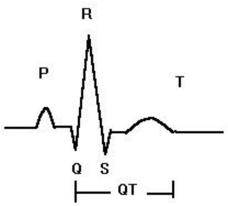
Subsets of common cancers

5% monogenic (bowel, ovary and breast cancers)

Medical Genetics a changing specialty
Heart disease

Rare forms due to single gene mutations

- Genes causing long QT
- Cardiomyopathy



Defibrillators, drugs etc

THE TIMES SATURDAY APRIL 29 2006 NEWS 5

Shock of 6am alarm bell killed nurse

A treatable disorder that claims up to 4,000 lives each year went unnoticed, **Will Pavia** and **Russell Jenkins** report

SUDDEN KILLER

Heart condition killed boy after school fight

David Sandham - died after fight

Challenge is getting doctors to recognise and refer

Genetic Medicine
a constantly changing discipline

In Genetic Medicine we have faced many of the issues being considered today

- Predictive testing
- Consent
- Privacy
- Communication
- Unexpected results

COMMENTARY

Predictive testing for Huntington's disease: the calm after the storm

Predictive testing for Huntington's disease has now been offered for longer than for any other genetic disease. A DNA marker linked to the disease was discovered in 1983,[1] and prenatal and predictive testing programmes for Huntington's disease began in 1986.[2,3] Predictive testing became technically simpler after the identification of the Huntington's disease gene[4] and the demonstration that the disease was always due to trinucleotide-repeat expansion,[5] because samples from numerous family relatives for linkage analysis became unnecessary.

Peter Harper and colleagues have recently described the information collected by the UK Huntington's disease

family planning, but to relieve the uncertainty of whether or not they carry the gene and to make life and career decisions.

What is remarkable is how this predictive test has become

primary and overriding responsibility of the geneticist is to the patient presenting for testing led to change to the international guidelines to include those at 25% prior risk.[11]

Another reason for the successful integration of this test into national health services has been universal access to the test irrespective of the ability to pay. By contrast, in the USA, despite the development of programmes in many states, patients may choose to be tested outside of established programmes for reasons of convenience, cost, or privacy. As a result, there are numerous stories of distress arising from results being given by telephone or without counselling.

An accepted standard of care—which includes pre-test counselling, disclosure of results in person, and the availability of post-test counselling and support[12]—has also

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Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, British Columbia V5Z 4H4, Canada

Viewpoint

Revealing false paternity: some ethical considerations

Anneke Lucassen, Michael Parker

Introduction

Advances in genetic research are allowing increasing numbers of conditions to be diagnosed at the molecular level. Confirmation of a genetic condition in one person almost invariably has implications for others: tests reveal information not only about the person tested but also

Lancet 2001; **357:** 1033–35

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where the information has reproductive implications for both partners. But what is current practice?

Current perspectives in clinical practice

The consensus emerging from the literature is not to tell the husband directly of the result. Only one report

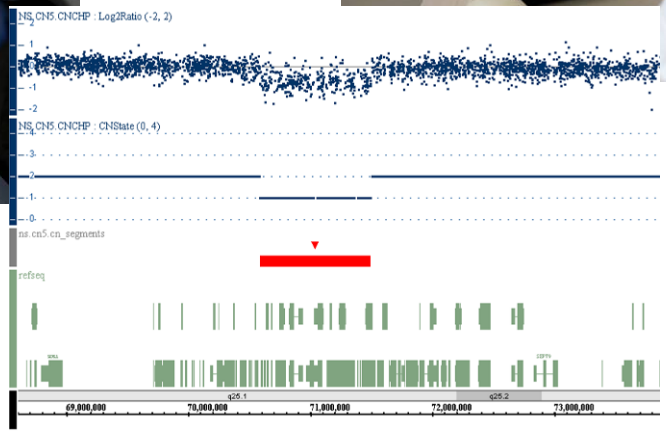
the consultation Mary reveals that Peter is not the father of her child. In this case, it would normally be considered inappropriate for the GP to inform Peter without Mary's permission. The same duty of respect for confidentiality ought to apply in the case of Sarah and John unless there is a morally significant difference between the cases.

There are in fact several key differences that make this argument rather less convincing in the case under consideration. Firstly, the information about paternity in

Challenges of new technologies and applications

- How Genetic medicine is changing
  - Array technologies used to investigate MR/multiple malformations
  - Pharmacogenetics
  - Treatment of genetic disease
  - Next generation sequencing

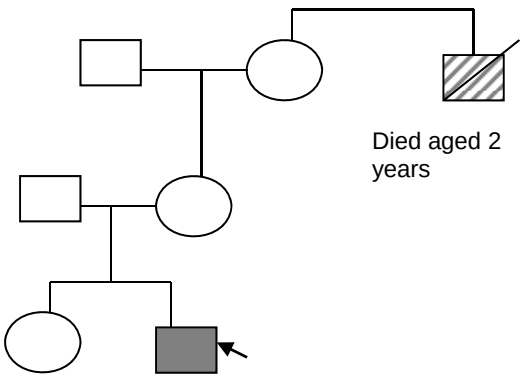
Better diagnosis and disease characterisation



For causes of developmental disorders

Case study

1982 Referral from Paediatric neurologist - *Please see this patient who has severe developmental delay and seizures. He has had the following investigations; TORCH screen, metabolic workup, chromosome analysis*



Severe retardation

Seizures

'mannersitic' behaviour

Unusual hair whorls

Prominent lips

Case study

Similar appearance to brother

Hand wringing

Lip smacking

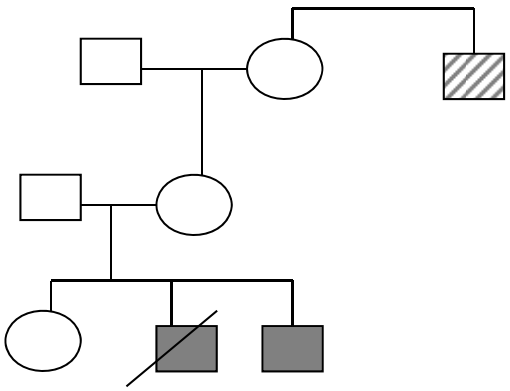
Severe LD

At 19 yrs 20 words

Investigations over the years

ATRX, ARX, MECP2, UBE3A, telomere screen, 1Mb array.

Entered in GOLD study



Sister counselled likely XLR inheritance

1 in 2 risk of being a carrier

Decision to have prenatal sexing and TOP of males

Pregnant Dec 2007

245kb deletion eliminates exons 2-15 of *MAOA* and

European Journal of Human Genetics (2010), 1–5

www.nature.com/ejhg

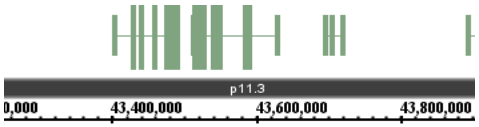
ARTICLE

Deletion of *MAOA* and *MAOB* in a male patient causes severe developmental delay, intermittent hypotonia and stereotypical hand movements

Annabel Whibley[1], Jill Urquhart[2], Jonathan Dore[2], Lionel Willatt[3], Georgina Parkin[3], Lorraine Gaunt[2], Graeme Black[2], Dian Donnai[2] and F Lucy Raymond[*,1]

Monoamine oxidases (MAO-A and MAO-B) have a key role in the degradation of amine neurotransmitters, such as dopamine, norepinephrine and serotonin. We identified an inherited 240 kb deletion on Xp11.3–p11.4, which encompasses both monoamine oxidase genes but, unlike other published reports, does not affect the adjacent Norrie disease gene (*NDP*). The brothers who inherited the deletion, and thus have no monoamine oxidase function, presented with severe developmental delay, intermittent hypotonia and stereotypical hand movements. The clinical features accord with published reports of larger microdeletions and selective MAO-A and MAO-B deficiencies in humans and mouse models and suggest considerable functional compensation between MAO-A and MAO-B under normal conditions.
European Journal of Human Genetics advance online publication, 19 May 2010; doi:10.1038/ejhg.2010.41

Keywords: monoamine oxidase; MAOA and MAOB; array CGH; X chromosome; abnormal hand movement



Clinical implications of diagnosis

April 2010. Admitted to hospital with chest infection. *Started on antibiotics. Sudden collapse – transferred to ICU. febrile, hypertensive and restless therefore sedated but no improvement ? Small cerebral bleed'*

Because he has no MAOA/MAOB he responds abnormally to certain foods and drugs – life threatening

Incidental findings with serious consequences

Predictive diagnosis of the cancer prone Li–Fraumeni syndrome by accident: new challenges through whole genome array testing

T Schwarzbraun,[1] A C Obenauf,[1] A Langmann,[2] U Gruber-Sedlmayr,[3] K Wagner,[1] M R Speicher,[1] P M Kroisel[1]

J Med Genet 2009;46:341–344.
doi:10.1136/jmg.2008.064972

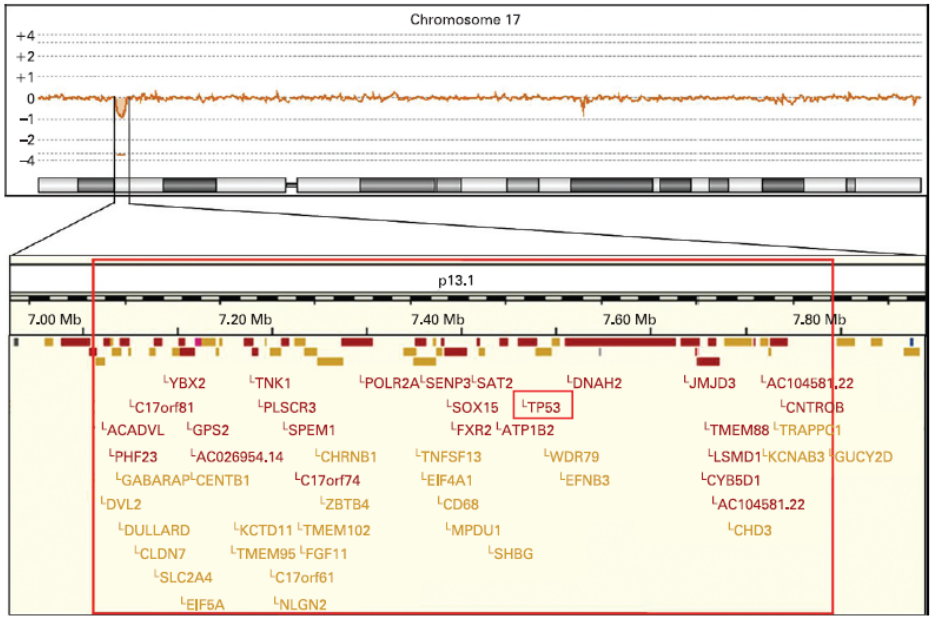
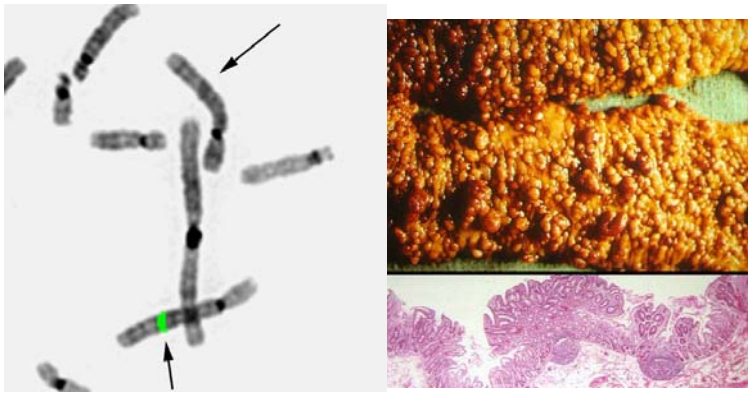


Figure 1 The top panel illustrates the array comparative genomic hybridisation profile of chromosome 17 demonstrating a small deletion in chromosome band 17p13.1. The lower panel depicts an enlargement of the deleted region. The exact localisation of the breakpoints was determined by sequence analysis. The *TP53* gene is almost at the centre of the deleted region. The *GUCY2D* gene is not included in the deleted region. However, the cis-regulatory elements are deleted, which explains the monoallelic expression of the gene and as a consequence the patient's cone–rod dystrophy 6.

Patient with 5q23.1 deletion includes APC gene



Challenges of new technologies and applications

Pharmacogenetics

Predict whether a specific drug (dose) will be effective or cause complications

Azathioprine

Used in RA, IBD, psoriasis, transplantation, leukaemia

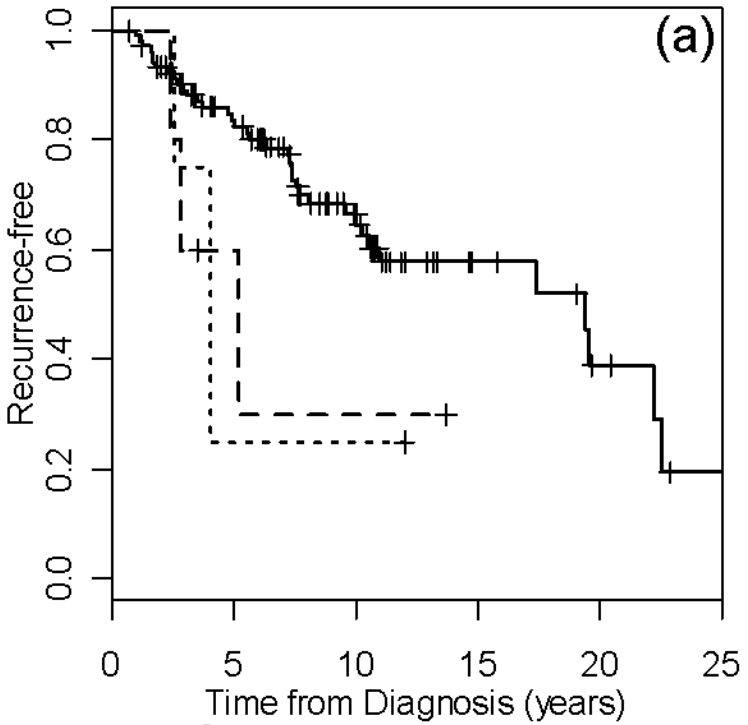
65,000 patients put on this drug every year in UK

TPMT (Thiopurine methyltransferase) testing detects;

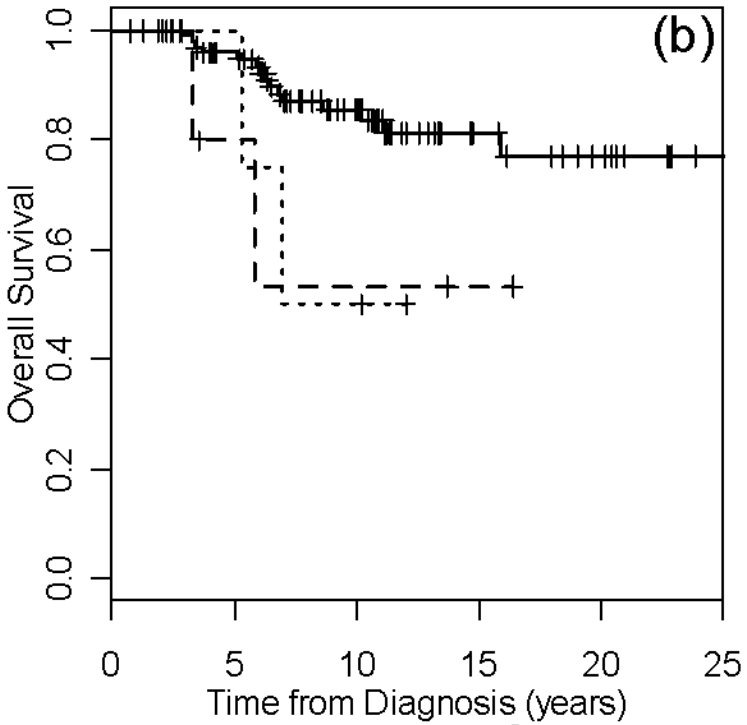
1 in 200 people who have the deficient genotype and develop severe bone marrow problems

Tamoxifen use in BRCA1/2 positive patients

*The effect of CYP2D6 genotype (*4 allele) and of CYP2D6 inhibitors*



Time to recurrence



Overall survival

Newman et al Clin Cancer Res. 2008;14(18):5913-8.

Will patients see the use of pharmacogenetic testing as drug rationing?

Treatment of Genetic Disease

Many options

Management of complications

Dietary management

Vitamin responsive metabolic diseases

Enzyme therapies

Organ transplantations

Protein/drug engineering

Gene therapy……..

Conventional pharmacology

Treatment Trials with already licensed drugs

- Marfan Syndrom
  - Losartan
- Tuberous sclerosis
  - Rapamycin
- Huntingtons disease
  - Dopamine stabilisers
  - Dimebon
- NF1 and NF2
  - Rapamycin and sorafenib
- FRAX
  - fenobam

Losartan, an AT1 Antagonist, Prevents Aortic Aneurysm in a Mouse Model of Marfan Syndrome

Jennifer P. Habashi,[1]* Daniel P. Judge,[2]* Tammy M. Holm,[1] Ronald D. Cohn,[1] Bart L. Loeys,[1] Timothy K. Cooper,[1,3] Loretha Myers,[1] Erin C. Klein,[1] Guosheng Liu,[3] Carla Calvi,[2] Megan Podowski,[2] Enid R. Neptune,[4] Marc K. Halushka,[4] Djahida Bedja,[3] Kathleen Gabrielson,[3] Daniel B. Rifkin,[5] Luca Carta,[6] Francesco Ramirez,[6] David L. Huso,[3] Harry C. Dietz[1,2]†

ORIGINAL ARTICLE

Sirolimus for Angiomyolipoma in Tuberous Sclerosis Complex or Lymphangioleiomyomatosis

John J. Bissler, M.D., Francis X. McCormack, M.D., Lisa R. Young, M.D., Jean M. Elwing, M.D., Gail Chuck, L.M.T., Jennifer M. Leonard, R.N., Vincent J. Schmithorst, Ph.D., Tal Laor, M.D., Alan S. Brody, M.D., Judy Bean, Ph.D., Shelia Salisbury, M.S., and David N. Franz, M.D.

Alzheimer's drug Dimebon helps Huntington's: study

(Reuters) - Dimebon, a pill being developed for Alzheimer's disease, helped people with Huntington's disease improve their thinking, learning and memory skills, U.S. researchers said on Monday.

HEALTH

Dimebon, made by Medivation Inc. under the generic name latrepirdine, appears to be safe for Huntington's patients and has minimal side effects, the researchers reported in the journal Archives of Neurology.

Dr. Karl Kieburtz of the University of Rochester in New York said his team chose to study Dimebon because it appeared to have an impact both on cognition and aging.

"In diseases like Huntington's disease where there is degeneration of the brain, one thing we look for is compounds that might favorably influence that and sometimes those compounds come out of things that can slow

JoAnne Allen
WASHINGTON
Mon Feb 8, 2010 5:47pm EST

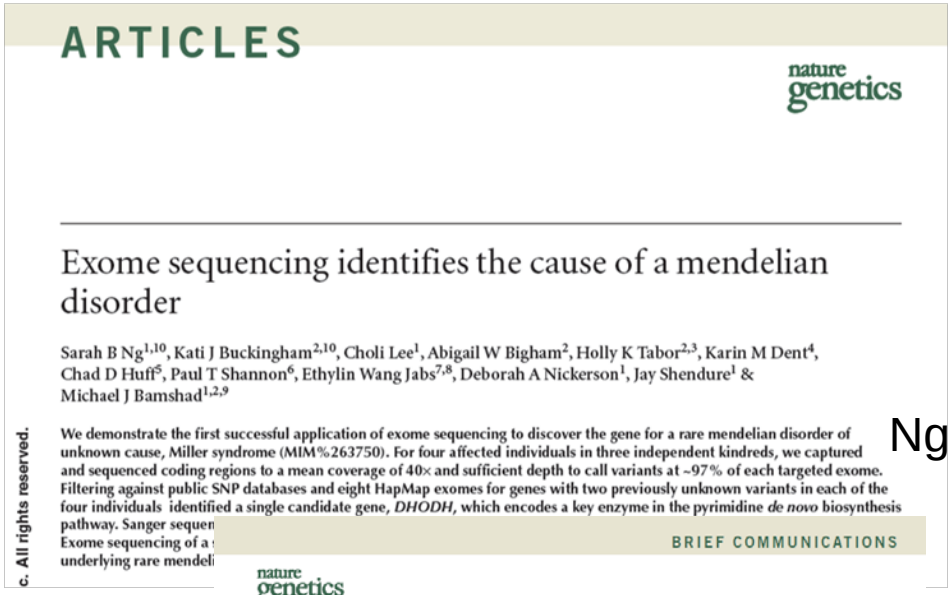
Related News
Alzheimer's drug Dimebon helps Huntington's - study
Mon, Feb 8 2010
Alzheimer's drug Dimebon helps Huntington's - study
Mon, Feb 8 2010
UPDATE 2-U.S. FDA staff questions small ChemGenex study
Mon, Feb 8 2010
Scientists find gene

le dose trial of fenobam in adults with fragile X syndrome

E Berry-Kravis,[1] D Hessl,[2,3] S Coffey,[3,8] C Hervey,[4] A Schneider,[2,3] J Yuhas,[2] J Hutchison,[5] M Snape,[5] M Tranfaglia,[6] D V Nguyen,[7] R Hagerman[3,8]

Practical Challenges for Clinical Genetic Services

Next generation sequencing



ARTICLES

nature genetics

Exome sequencing identifies the cause of a mendelian disorder

Sarah B Ng[1,10], Kati J Buckingham[2,10], Choli Lee[1], Abigail W Bigham[2], Holly K Tabor[2,3], Karin M Dent[4], Chad D Huff[5], Paul T Shannon[6], Ethylin Wang Jabs[7,8], Deborah A Nickerson[1], Jay Shendure[1] & Michael J Bamshad[1,2,9]

We demonstrate the first successful application of exome sequencing to discover the gene for a rare mendelian disorder of unknown cause, Miller syndrome (MIM%263750). For four affected individuals in three independent kindreds, we captured and sequenced coding regions to a mean coverage of 40× and sufficient depth to call variants at ~97% of each targeted exome. Filtering against public SNP databases and eight HapMap exomes for genes with two previously unknown variants in each of the four individuals identified a single candidate gene, *DHODH*, which encodes a key enzyme in the pyrimidine *de novo* biosynthesis pathway. Sanger sequen
Exome sequencing of a
underlying rare mendeli

Miller syndrome

Ng, S.B. *et al. Nat. Genet.* **42**, 30–35 (2010).

BRIEF COMMUNICATIONS

nature genetics

De novo mutations of *SETBP1* cause Schinzel-Giedion syndrome

Alexander Hoischen[1,14], Bregje W M van Bon[1,14], Christian Gilissen[1,14], Peer Arts[1], Bart van Lier[1], Marloes Steehouwer[1], Petra de Vries[1], Rick de Reuver[1], Nienke Wieskamp[1], Geert Mortier[2], Koen Devriendt[3], Marta Z Amorim[4], Nicole Revencu[5], Alexa Kidd[6], Mafalda Barbosa[7], Anne Turner[8], Janine Smith[9], Christina Oley[10], Alex Henderson[11], Ian M Hayes[12], Elizabeth M Thompson[13], Han G Brunner[1], Bert B A de Vries[1] & Joris A Veltman[1]

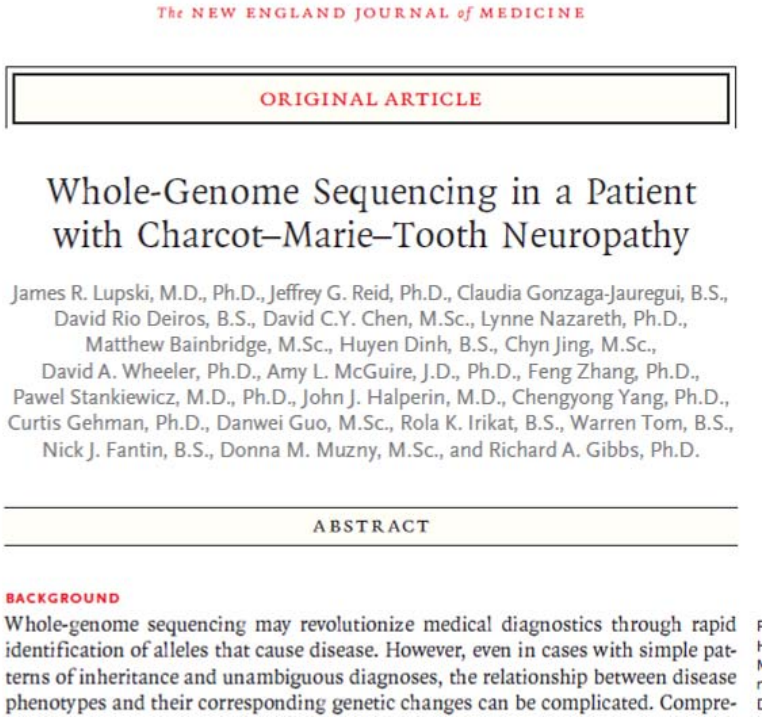
Schinzel-Giedion syndrome is characterized by severe mental retardation, distinctive facial features and multiple congenital malformations; most affected individuals die before the age of ten. We sequenced the exomes of four affected individuals (cases) and found heterozygous *de novo* variants in *SETBP1* in all four. We also identified *SETBP1* mutations in eight additional cases using Sanger sequencing. All mutations clustered to a highly conserved 11-bp exonic region, suggesting a dominant-negative or gain-of-function effect.

We sequenced the exomes (37 Mb of genomic sequence, targeting ~18,000 genes) of four unrelated individuals with Schinzel-Giedion syndrome to a mean coverage of 43-fold (**Supplementary Table 1**, **Supplementary Figs. 1** and **2**). The exomes of all four individuals were enriched using the SureSelect human exome kit (Agilent) and were subsequently sequenced using one quarter of a SOLiD sequencing slide (Life Technologies). A total of 2.7–3.0 gigabases of mappable sequence data were generated per individual, with 65–72% of bases mapping to the targeted exome (**Supplementary Table 1**). On average, 85% of the exome was covered at least tenfold, and 21,800 genetic variants were identified per individual, including 5,351 nonsynonymous changes. A number of prioritization steps were applied to reduce this number and to identify the potentially pathogenic mutations, similar to the methods used in previous studies[4,5] (**Supplementary Table 2**). A comparison with the NCBI dbSNP build 130 as well as with recently released SNP data from other groups and in-house SNP data (see **Supplementary Note**) showed that >95% of all variants investigated here were previously reported SNPs and cannot explain a genetically dominant disease. We focused on the 12 genes for which all four individuals studied carried variants and found that only two genes showed variants at different genomic positions, strengthening the likelihood that these variants are causative and not simply unidentified SNPs. One of these two candidate genes, *CTBP2*, was excluded

Schinzel-Gideon syndrome

Hoischen et al *Nature Genetics* aol pub May 2010

Personal genomes



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Whole-Genome Sequencing in a Patient with Charcot–Marie–Tooth Neuropathy

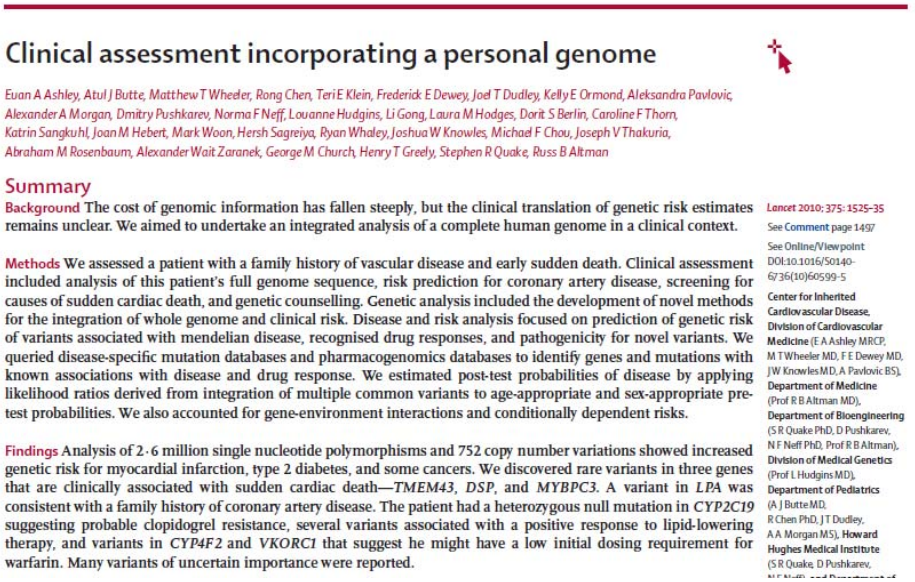
James R. Lupski, M.D., Ph.D., Jeffrey G. Reid, Ph.D., Claudia Gonzaga-Jauregui, B.S., David Rio Deiros, B.S., David C.Y. Chen, M.Sc., Lynne Nazareth, Ph.D., Matthew Bainbridge, M.Sc., Huyen Dinh, B.S., Chyn Jing, M.Sc., David A. Wheeler, Ph.D., Amy L. McGuire, J.D., Ph.D., Feng Zhang, Ph.D., Pawel Stankiewicz, M.D., Ph.D., John J. Halperin, M.D., Chengyong Yang, Ph.D., Curtis Gehman, Ph.D., Danwei Guo, M.Sc., Rola K. Irikat, B.S., Warren Tom, B.S., Nick J. Fantin, B.S., Donna M. Muzny, M.Sc., and Richard A. Gibbs, Ph.D.

ABSTRACT

BACKGROUND

Whole-genome sequencing may revolutionize medical diagnostics through rapid identification of alleles that cause disease. However, even in cases with simple patterns of inheritance and unambiguous diagnoses, the relationship between disease phenotypes and their corresponding genetic changes can be complicated. Compre-

NEJM April 1st 2010



Clinical assessment incorporating a personal genome

Euan A Ashley, Atul J Butte, Matthew T Wheeler, Rong Chen, Teri E Klein, Frederick E Dewey, Joel T Dudley, Kelly E Ormond, Aleksandra Pavlovic, Alexander A Morgan, Dmitry Pushkarev, Norma F Neff, Louanne Hudgins, Li Gong, Laura M Hodges, Dorit S Berlin, Caroline F Thorn, Katrin Sangkuhl, Joan M Hebert, Mark Woon, Hersh Sagreiya, Ryan Whaley, Joshua W Knowles, Michael F Chou, Joseph V Thakuria, Abraham M Rosenbaum, Alexander Wait Zaranek, George M Church, Henry T Greely, Stephen R Quake, Russ B Altman

Summary

Background The cost of genomic information has fallen steeply, but the clinical translation of genetic risk estimates remains unclear. We aimed to undertake an integrated analysis of a complete human genome in a clinical context.

Methods We assessed a patient with a family history of vascular disease and early sudden death. Clinical assessment included analysis of this patient's full genome sequence, risk prediction for coronary artery disease, screening for causes of sudden cardiac death, and genetic counselling. Genetic analysis included the development of novel methods for the integration of whole genome and clinical risk. Disease and risk analysis focused on prediction of genetic risk of variants associated with mendelian disease, recognised drug responses, and pathogenicity for novel variants. We queried disease-specific mutation databases and pharmacogenomics databases to identify genes and mutations with known associations with disease and drug response. We estimated post-test probabilities of disease by applying likelihood ratios derived from integration of multiple common variants to age-appropriate and sex-appropriate pre-test probabilities. We also accounted for gene-environment interactions and conditionally dependent risks.

Findings Analysis of 2·6 million single nucleotide polymorphisms and 752 copy number variations showed increased genetic risk for myocardial infarction, type 2 diabetes, and some cancers. We discovered rare variants in three genes that are clinically associated with sudden cardiac death—*TMEM43*, *DSP*, and *MYBPC3*. A variant in *LPA* was consistent with a family history of coronary artery disease. The patient had a heterozygous null mutation in *CYP2C19* suggesting probable clopidogrel resistance, several variants associated with a positive response to lipid-lowering therapy, and variants in *CYP4F2* and *VKORC1* that suggest he might have a low initial dosing requirement for warfarin. Many variants of uncertain importance were reported.

Lancet 2010; 375: 1525–35

See **Comment** page 1497

See Online/Viewpoint

DOI:10.1016/S0140-6736(10)60599-5

Center for Inherited Cardiovascular Disease, Division of Cardiovascular Medicine (E A Ashley MRCP, M T Wheeler MD, F E Dewey MD, J W Knowles M D, A Pavlovic BS), **Department of Medicine** (Prof R B Altman MD), **Department of Bioengineering** (S R Quake PhD, D Pushkarev, N F Neff PhD, Prof R B Altman), **Division of Medical Genetics** (Prof L Hudgins MD), **Department of Pediatrics** (A J Butte MD, R Chen PhD, J T Dudley, A A Morgan MS), **Howard Hughes Medical Institute** (S R Quake, D Pushkarev,

Lancet May 1st 2010

Issues to be considered in Clinical Practice in whole genome sequencing

- Initial consent
  - Service
  - Research – consent to feedback?
- Finding linked to reason for testing or research
- Finding incidental to reason for testing/research

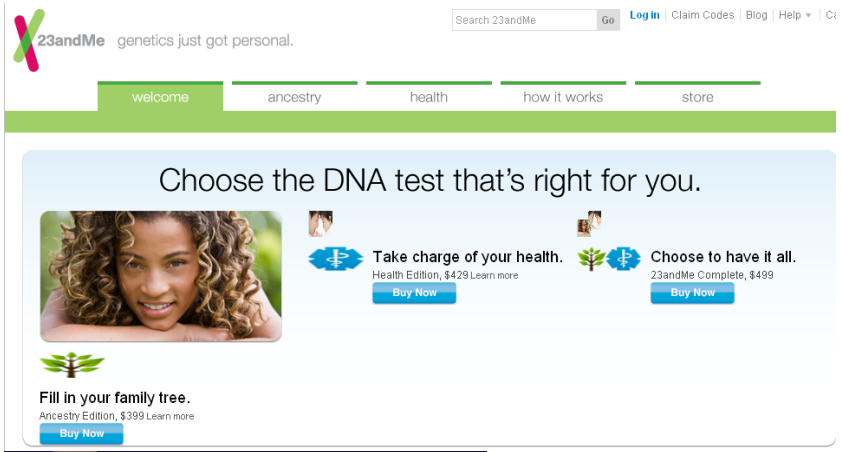
Issues to be considered in Clinical Practice in whole genome sequencing

- Which variants to be reported
- Verification of finding from research lab in QA assured lab

- Who feeds back
- Implications for health/screening etc
- Implications for family members
- Testing children

Practical challenges

The rise of Direct to Consumer testing

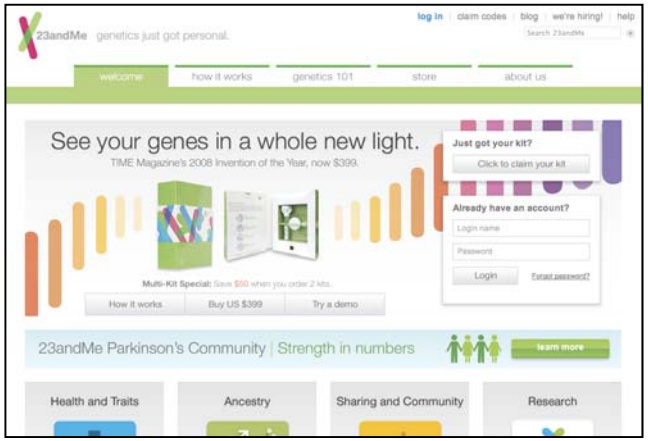


Potential impact on clinical genetic services

The 'Worried well' using limited services

Practical challenges
The rise of Direct to Consumer testing

- ‘Health screening’ with SNPs etc



- Whole genome screening

What about the impact of the $1000 genome?

Concerns about DTC testing

LETTERS

Autism genome-wide copy number variation reveals ubiquitin and neuronal genes

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Autism spectrum disorders (ASDs) are childhood neurodevelopmental disorders with complex genetic origins[1–4]. Previous studies focusing on candidate genes or genomic regions have identified several copy number variations (CNVs) that are associated with an increased risk of ASDs[5–8]. Here we present the results from a whole-genome CNV study on a cohort of 859 ASD cases and 1,409 healthy children of

in one study often fail to replicate in other studies, and a consistent picture of susceptibility loci in autism is still lacking. Some telling clues about ASD genetics arose from recent studies on CNVs[9], including the association of *de novo* CNVs with ASDs[4]. Although *de novo* CNVs that disrupt specific genes may contribute to the pathogenesis of ASDs, heritable CNVs are much more common but have been less

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ARTICLES

Common genetic variants on 5p14.1 associate with autism spectrum disorders

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Autism spectrum disorders (ASDs) represent a group of childhood neurodevelopmental and neuropsychiatric disorders characterized by deficits in verbal communication, impairment of social interaction, and restricted and repetitive patterns of interests and behaviour. To identify common genetic risk factors underlying ASDs, here we present the results of genome-wide association studies on a cohort of 780 families (3,101 subjects) with affected children, and a second cohort of 1,204 affected subjects and 6,491 control subjects, all of whom were of European ancestry. Six single nucleotide polymorphisms between cadherin 10 (*CDH10*) and cadherin 9 (*CDH9*)—two genes encoding neuronal cell-adhesion

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Daily Mail
WEDNESDAY, APRIL 29, 2009 www.dailymail.co.uk DAILY NEWSPAPER OF THE YEAR 50p
MONEY MAIL STARTS PAGE 38

Manicures, diets and already dreaming of cosmetic surgery at ten **RISE OF THE CHILD WOMEN**

PAGES 28-29

Genetic scientists hail 'monumental' breakthrough that could help millions

HAVE WE FOUND KEY TO AUTISM?

SCIENTISTS have pinpointed rogue genes that could unlock the riddle of autism.

By Fiona MacRae
Science Reporter

The breakthrough has been hailed as a 'monumental achievement' that could revolutionise understanding and treatment of the condition.

Experts have compared it to the pivotal cancer research of the 1970s, which began unravelling the disease's genetic causes.

Autism and related conditions such as Asperger's syndrome affect at least one in 100 UK children, and some research puts the figure as high as one in 60. Even the lower estimate is ten times the level of 30 years ago.

With the causes unclear, children are usually treated with a combination of speech, behavioural and other therapies. Drugs can be given to control symptoms such as aggression or hyperactivity, but these cannot be cured.

Now three major studies have identified specific genetic links to autism, related to the development and 'wiring' of the brain.

Last night a spokesman for the National Autistic Society said the landmark research could pave the way to improving life for hundreds of thousands of Britons with autism

Turn to Page 4

Iain and Dawn Askham: Four-day delay in isolating them

Swine flu newly weds could have infected hundreds

SEE PAGES 6-7

Daily Mail | 29 April 2009

THE INDEPENDENT SCIENCE

Autism and genetics: A breakthrough that sheds light on a medical mystery

By Steve Connor, Science Editor

Thursday, 10 June 2010

Scientists have discovered the first significant link between autism and DNA, in a study that could revolutionise understanding of this disturbing behavioural disorder which affects more than half-a-million Britons.

The researchers believe the changes they have found to the genetic make-up of autistic children play a significant role in causing the developmental illness. Their findings could eventually lead to early diagnostic tests for autism and new forms of treatment, based on

doi:10.1038/nature09146 nature

LETTERS

Functional impact of global rare copy number variation in autism spectrum disorders

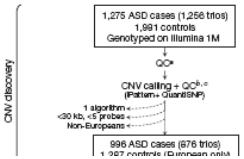
A list of authors and their affiliations appears at the end of the paper.

The autism spectrum disorders (ASDs) are a group of conditions characterized by impairments in reciprocal social interaction and communication, and the presence of restricted and repetitive behaviours[1]. Individuals with an ASD vary greatly in cognitive development, which can range from above average to intellectual disability[2]. Although ASDs are known to be highly heritable (~90%)[3], the underlying genetic determinants are still largely unknown. Here we analysed the genome-wide characteristics of rare (<1% frequency) copy number variation in ASD using dense genotyping arrays. When comparing 996 ASD individuals of European ancestry to 1,287 matched controls, cases were found to carry a higher global burden of rare, genic copy number variants (CNVs) (1.19 fold, $P = 0.012$), especially so for loci previously implicated in either ASD and/or intellectual disability (1.69 fold, $P = 3.4 \times 10^{-4}$). Among the CNVs there were numerous ***de novo*** and inherited events, sometimes in combination in a given family, implicating many novel ASD genes such as ***SHANK2, SYNGAP1, DLGAP2*** and the X-linked ***DDX53–PTCHD1*** locus. We also discovered an enrichment of CNVs disrupting functional gene sets involved in cellular proliferation, projection and motility, and GTPase/Ras signalling. Our results reveal many new genetic and functional targets in ASD that may lead to final connected pathways.

Twin and family studies indicate a predominantly genetic basis for ASD susceptibility and provide support for considering these disorders as a clinical spectrum. Some 5–15% of individuals with an

called by both algorithms in an individual (Fig. 1, Supplementary Tables 1–3 and Supplementary Fig. 3). This stringent data set of 5,478 rare CNVs in 996 cases and 1,287 controls of European ancestry (Supplementary Table 4) had the following characteristics: (1) CNV present at <1% frequency in the total sample (cases and controls); (2) CNV ≥30 kb in size (because >95% of these could be confirmed); and (3) all CNVs further verified using combined evidence from the PennCNV algorithm[18] and child–parent intensity fold changes, genotype proportions (to verify deletions) and visual inspection (for chromosome X).

We assessed the impact of rare CNV in cases compared to controls using three primary measures of CNV burden: the number of CNVs per individual, the estimated CNV size, and the number of genes affected by CNVs (Table 1). No significant difference was found in the former two



Practical Challenges for Clinical Genetic Services

Medical Geneticists must get back in the ‘mainstream’ of medicine

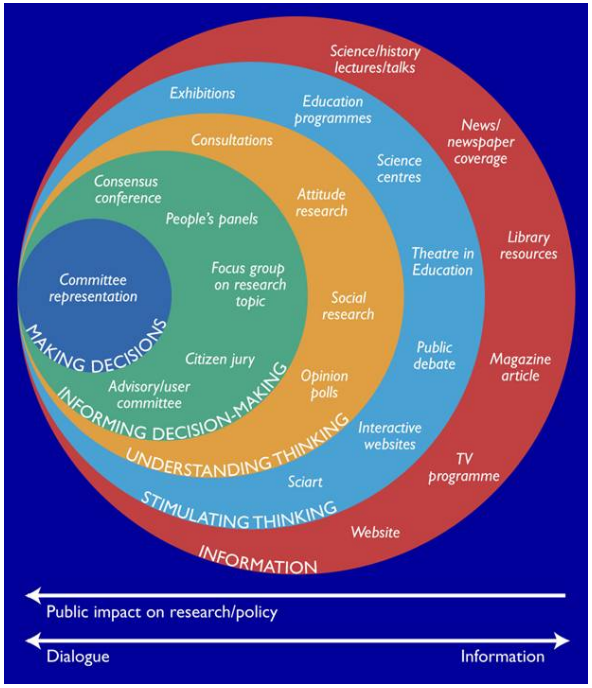
Patients with rare diseases need continuing care and treatment, their relatives need our services

We must embrace the new technologies and ensure they are used appropriately for our patients

We should engage with patient groups, the public and media

Public engagement

Public engagement 'onion'
*For a sustainable model of public engagement and meaningful dialogue, need to support **all** layers*



Target Groups

- Schools and young people
- Public
  - Broad approach (exhibitions, TV, electronic media)
  - In more depth (polls and debates)
  - Healthcare professionals and allied groups
- Patient groups and cohorts