Creating a Translation Loop for Genomic Medicine

Outcomes Data from Clinical Applications:
Bioresources Linked to e-health Records

in Scotland

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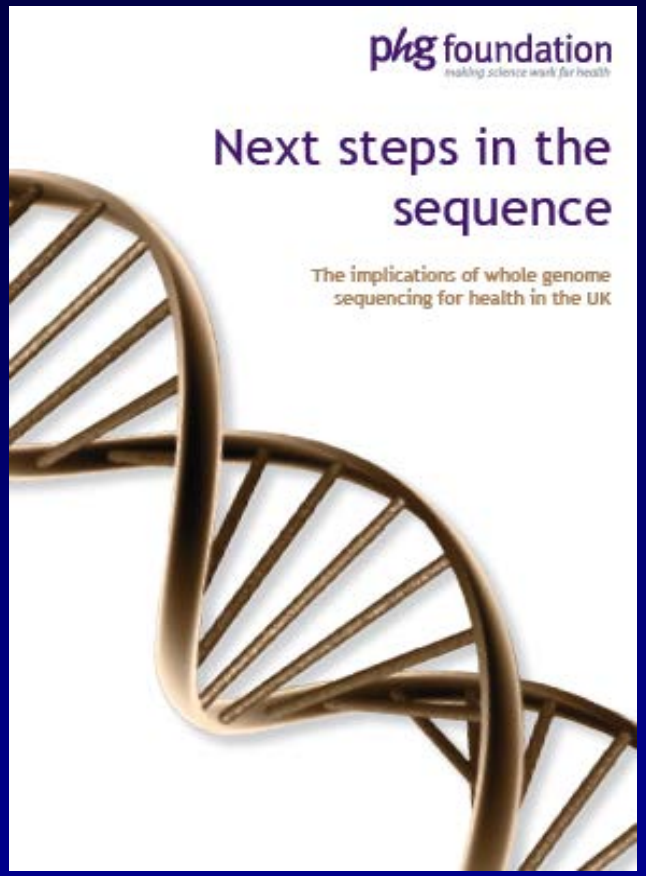
From yesterday…..

- “ need to do the studies to provide the evidence base for clinical utility”

- “ If you put things in bin 2 you need to state clearly what data are needed to get it out of bin 2 “

- “ to have better data to establish whether a very rare variant is likely to be causal is the priority “

- *The NHS presents a wonderful opportunity to implement WGS in a way that is evidence-based, systematic, and efficient and can collect evidence prospectively.*
- *How can NHS data be used to answer relevant questions in the translation loop ?*
- *Use MODY as an example*

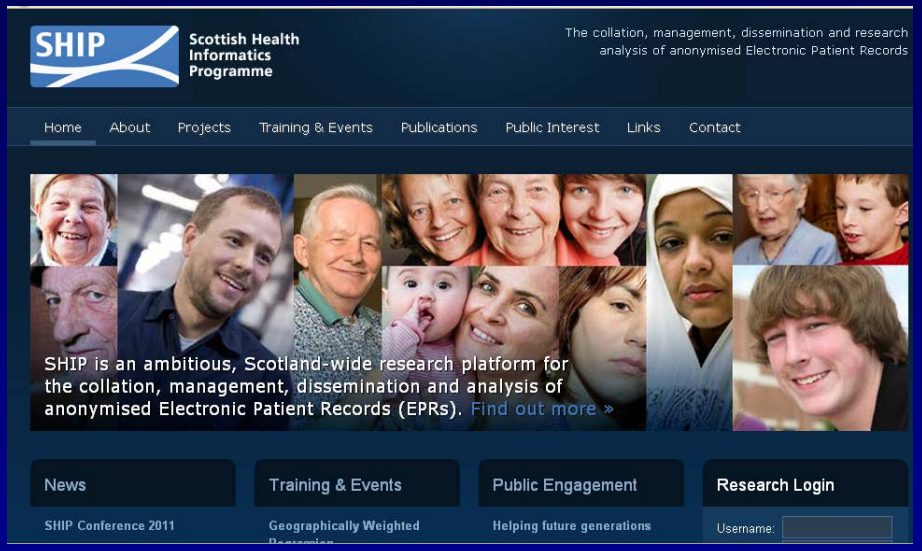


The next 10 minutes …

- Electronic health care data available for research in Scotland
- Bioresources linked to diabetes and other health records in Scotland
- Using MODY (monogenic diabetes) as an example:
  - Consider how e-health records containing genetic data or linked to DNA bioresources are contributing to resolving these questions

Data available for Research

- Unique health care identifier –CHI number on all health related encounters
- Permits linkage between available datasets
- Examples Scottish morbidity Records hospital admissions, cancer , maternal and child, psychiatric
- Primary Care data
- Governance framework for research access to data : Scottish Health Informatics Programme



generation SCOTLAND

	Scottish Family Health Study	Genetic Health in the 21st Century	Donor DNA Databank (3D)
Cohort	Family Based	Representative Control	Controls
Numbers	>24,000 Family Members - Extensive Family Pedigrees	2,000 Unrelated Scottish Individuals	5,000 Individuals
Samples	Blood, Serum, DNA, Urine, Cryo-preserved Blood and Biochemical Data	Blood, Plasma, DNA, Cells	DNA, Plasma
Data	Intensive Phenotype, Clinical Measures, Mental Health & Cognition	Moderate Phenotype Clinical Measures, Personality & Cognition	Minimal Phenotype
Follow-up	Consent for Re-contact and Record Linkage	Consent for Re-contact and Record Linkage	Anonymised

Linkage to hospital records back to 1981, death Ca registry, birth records, national prescribing dataset, lab data etc etc

GS:SFHS Phenotype and Samples

Personal information
- **Pedigree**
- **Demographics**

Clinic measurements
- **Body Measurement**
- **Ankle-Brachial Pressure Index**
- **Spirometry**
- **ECG**
- **Cognitive testing***
- **SCID (major mental Disorders)***
- **Psychometric testing***

Biological Samples
- **DNA**
- **Serum**
- **Cryopreserved blood**
- **Urine**

Biological samples data
- **Biochemistry**
- **Genotype**

***validated methodology**

Questionnaire
- Family History
- Family Health
- Medications
- Operations
- Chest Pain*
- Musculoskeletal
- Chronic Pain*
- Exercise
- Thoughts & experiences (SPQ-B, MDQ)*
- Diet
- Alcohol
- Smoking
- Education
- Occupation
- Household
- Women's Health

Heart Disease
Stroke
High Blood Pressure
Diabetes
Alzheimer's Disease
Parkinson's Disease
Depression
Breast Cancer
Bowel Cancer
Lung Cancer
Prostate Cancer
Hip Fracture
Osteoarthritis
Rheumatoid Arthritis
Asthma
COPD

Scottish Care Information - Diabetes Collaboration Anonymised Linkage to Routine Datasets for Research Purposes

Primary Care including prescriptions

Hospitals

Podiatry

Community nursing

National retinopathy screening programme

SCI-DC

Federated database
Captures > 95% of Patients with DM in Scotland's 5 million population
N~250,000

Data are linked through unique record number (CHI) and by probabalistic linkage

ICD coded Hospital admission Scottish Morbidity Record 01

ICD coded GRO-Death data

Scottish Renal Register

National e-prescribing

National lab database SCI-store

Scottish Care Information - Diabetes Collaboration
Creating Bioresources Linked to the Data

UK WT GCC/ Go-Darts
9000 Type 2 and general population controls in Tayside Scotland
PI: A Morris

Type 1 Bioresource 9000Scotland Wide adults with type 1 DM
PI : H Colhoun

SCI-DC

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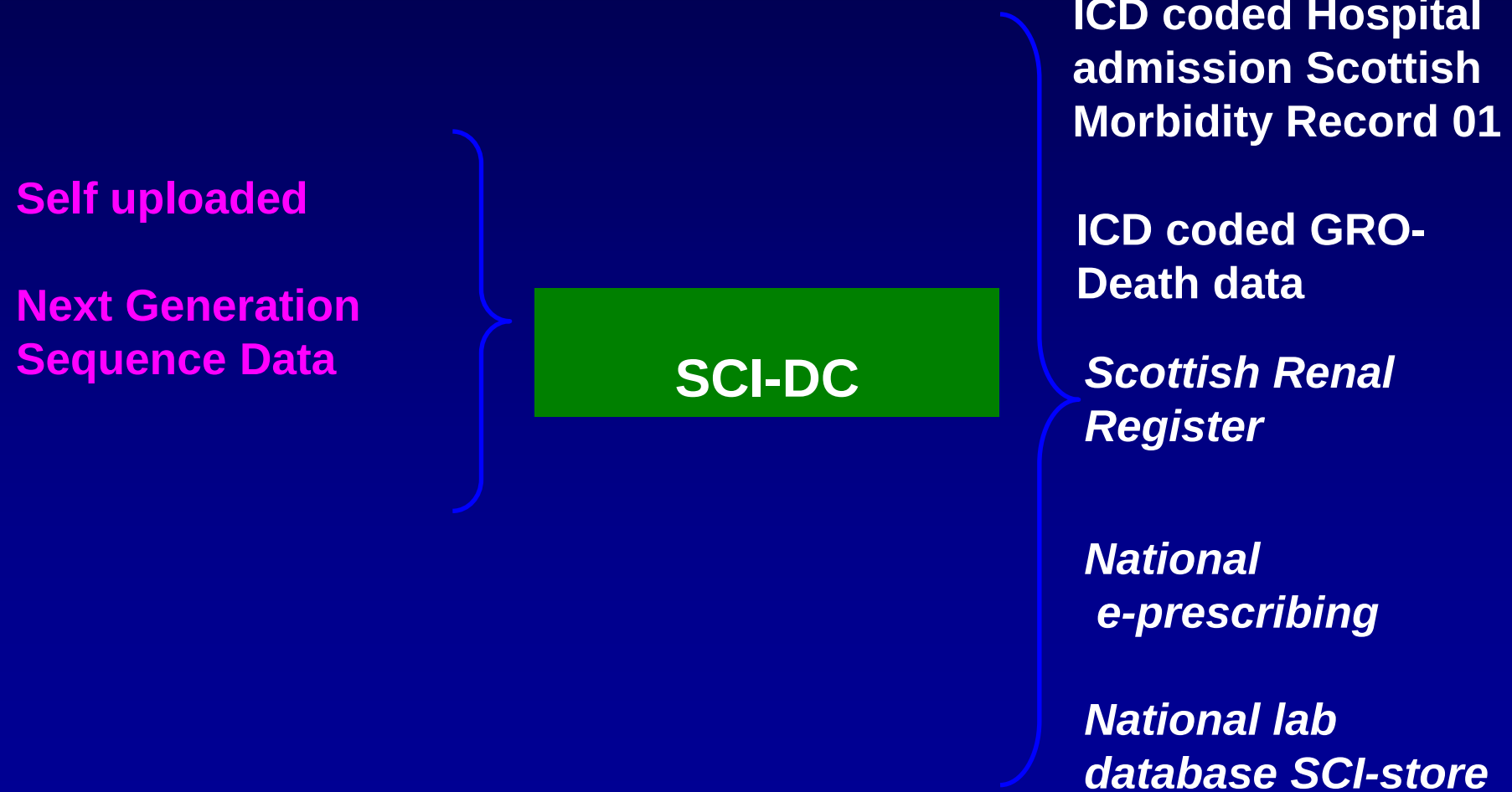
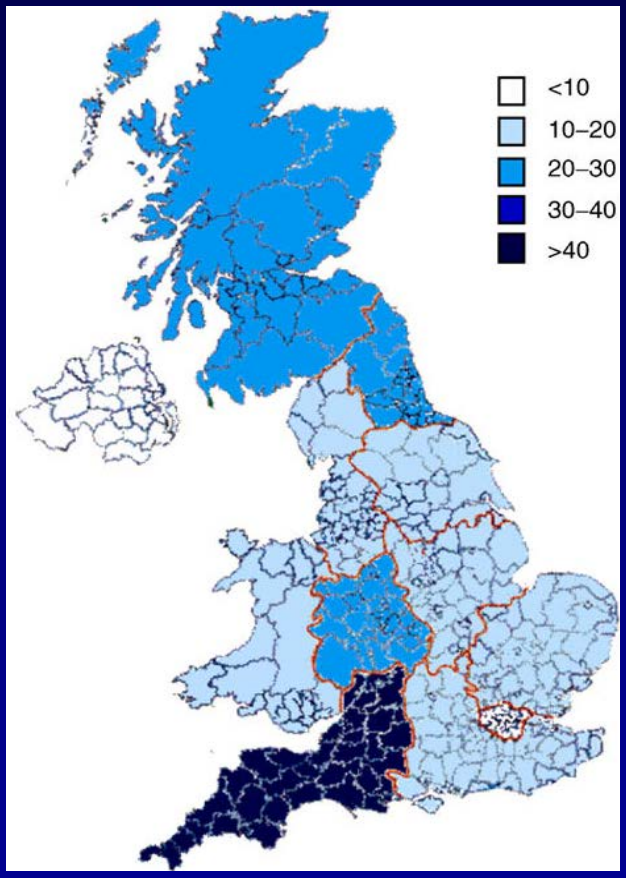


Maturity onset Diabetes in the Young MODY: An example of an unactioned actionable variant

- Since the 1990's it has been known that 80% of Monogenic diabetes is due to AD mutations in GCK, HNF-1-α and HNF -4-α
- A diagnosis of these mutations has very significant implications for patients i.e. that insulin not required until late stage in many cases.
- But we still do not screen all apparent type 1 or youth onset type 2 patients
- Hattersley showed that the cases/million population varied enormously within the UK (5.3-48.9) with detection rate <20%



Shields B et al *Diabetologia (2010) 53:2504–2508*

Why is Knowledge about MODY not Actioned ?

- Rare (~2% of all DM) and difficult to differentiate clinically from type 1 and type 2 DM
- Lack of clinical awareness
- low yields and high cost of diagnostic test - currently ~ £700
- Lack of central funding for testing- not on UKGTN Directory of tests : Sequencing and (Multiplex Ligation-dependent Probe Amplification) are needed since exon and whole gene deletions can be present so
- Test not available at local lab: currently Exeter Lab

Key Outstanding Bottlenecks / Issues

- What is the best strategy for diagnosing MODY?
- E.g. Family Hx then c-peptide then antibodies then genetic test?
  - feasibility/ uptake, genetic counselling needs, yield, change in DM control and outcomes, cost effectiveness, patient satisfaction,
- Are there biomarkers that are useful in stratifying patients for genetic testing ? c-peptide, hsCRP, N-Glycan branching?
- How can clinical decision making about genetic testing be improved through the EHR?
- Can we harness existing GWAS data to establish long stretches of IBD between cases and thereby reduce need for sequencing?
- Or should we just wait longer until sequencing gets cheaper ?

How can clinical decision making about genetic testing be improved through the EHR and related Bioresource?

- Randomised comparison of yield of cases when Clinical decision making support function added to EHR versus not added to prompt potential MODY screening
  - Improved capture of family history, age at onset, OGTT result, DKA history
  - Algorithm to prompt c-peptide and GAD assessment based on Family history

Effectiveness of Strategies and Biomarkers for MODY

- Use the EHR dataset for recruitment and for past Hx variables
- Urinary–C-peptide/ creatinine ratio as initial test of prioritising for genetic testing :collaboration of SDRN bioresource and UNITED study (PI Andrew Hattersley)
- Predictive utility of hsCRP for prioritising for genetic testing
- Utility of glycomic markers in screening : GWAS showed that HNF1α is a master regulator of plasma protein fucosylation *Lauc et al PLOS Genetics Dec 10*
- Examine outcomes: HbA1c change, ultimately complication rates

Can we harness existing GWAS data to infer IBD between cases and thereby reduce need for sequencing?

- In the future we may have a system where extensive use of a GWAS data or extensive sequence information exists
- So now we can use bioresources linked to e-health data be to answer this question
  - In a relatively isolated population can new cases of MODY be diagnosed based on IBD sharing at known MODY loci with known MODY cases in that population ?

Summary and Conclusions

- We need to harness the power of EHRs linked to bioresources to complete the translational loop
- Clinical validity and utility can be examined
- Trials of methods for initiating detection and algorithms for detection can be facilitated
- Need demonstration projects and systematic effort with WGS data held as research data with minimal reporting back initially
- Effects of reporting back should be formally evaluated so as to inform utility

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