8th Mackenzie Lecture

The Limits of Personalised Medicine: Epidemiological Reflections

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School of Social and Community Medicine
University of Bristol
Sir James Mackenzie (aged about 70)

The young apprentice chemist, 1869
Mackenzie J. A Defence of the Thesis that “The opportunities of the general practitioner are essential for the investigation of disease and the progress of medicine”. Int J Epidemiol 2012;41: 1507-1518.
Commentary: A thesis that still warrants defence and promotion

Blair H Smith,1* Bruce Guthrie,2 Frank M Sullivan1 and Andrew D Morris4

1Population Science, Medical Research Institute, University of Dundee, Dundee, Scotland, UK 2Primary Care, Medical Research Institute, University of Dundee, Dundee, Scotland, UK 3General Practice, Medical Research Institute, University of Dundee, Dundee, Scotland, UK 4Diabetic Medicine, Medical Research Institute, University of Dundee, Dundee, Scotland, UK

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Introduction

Sir James Mackenzie (1852 to 1925) is known as ‘the father of general practice-based research’.1 His and it is at St Andrews University that his heart remains (literally, in the anatomy department).2 Although he had re-located his professional and academic base to London when his career took off.

Commentary: James MacKenzie 1921, still relevant in 2012

Richard Baker

Department of Health Sciences, University of Leicester, Leicester, UK. E-mail: rb14@le.ac.uk

Accepted 1 August 2012

Commentary: Sir James Mackenzie (1853–1925): An ambiguous pioneer for research in primary care

Julian Tudor Hart

University of Swansea Medical School, College of Medicine, Grove Building, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK. E-mail: julian.tudorhart@yahoo.co.uk

Accepted 9 October 2012

Sir James Mackenzie is generally accepted as the founder of research by general practitioners in Great Britain, studying their own patients where and how they actually live. His pioneering work on arrhythmias was a foundation for modern cardiology, con-
The St Andrews Institute for Clinical Research
It has been suggested that he chose to go to St Andrews more for retirement and the golfing facilities than the research opportunities: he was a keen golfer all his life.

MacNaughton J. Medical History 2002;46:549-568
GONE GOLFING
Sir James Mackenzie’s Heart

Fig. 4.—Section of the stem of the right coronary artery, showing the lumen irregularly narrowed by thickening of the sub-endothelial and middle layers, and patches of degeneration and calcification.
(A) Lumen. (B) Endothelial tunic. (C) Sub-endothelial tunic. (D) Patches of degeneration and calcification in middle tunic. (E) Large calcified area. (F) Adventitial tunic.

Proposed work of the St Andrews Institute for Clinical Research

To investigate disease before the occurrence of any structural change in any organ of the body, with the view of providing a diagnosis at a period earlier than is possible by the methods now in use and in order to obtain knowledge of the circumstances that favour the onset of disease.

Mair A. Sir James Mackenzie MD 1853 – 1925. General Practitioner. 1973
“Mackenzie was naïve to think [the appeal] would have the desired effect. There was no doubt about his own popular image and appeal, but did the wider public get his message? Moreover, Scotland traditionally thrifty and tight-fisted, was not London”

One of the first cars in Burnley, Mackenzie on his rounds
… in the surgical treatment of gastric ulcer… I have seen patients greatly benefited by the operation; I have seen some made worse by the operation, and I have seen patients die in consequence of the operation. These results are due to an absence of a knowledge of prognosis

“For more than one hundred years it has been recognized that digitalis had a beneficial action in certain forms of heart disease, but no definite knowledge existed as to the kind of heart disease which benefited, so that every person supposed to have a heart affection was given digitalis. Careful investigation has revealed that the drug is of use in only a small percentage of cases, and that of a particular kind. We can now recognize with fair certainty the cases where it will have a good effect and those cases in which it is of no use”.

PPPP (P) Medicine

Predictive
Preventive
Personalized
Participatory
(Population perspective)


A Hypothetical case in 2010

“John, a 23-year-old college graduate, is referred to his physician because a serum cholesterol level of 255 mg per deciliter was detected in the course of a medical examination required for employment. He is in good health but has smoked one pack of cigarettes per day for six years..... To obtain more precise information about his risks of contracting coronary artery disease and other illnesses in the future, John agrees to consider a battery of genetic tests that are available in 2010”.

Collins F. Shattuck Lecture — Medical and societal consequences of the human genome project. NEJM 1999; 341: 28-37.
### Results of genetic testing in a hypothetical patient in 2010

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*HPC1, HPC2, and HPC3 are the three genes for hereditary prostate cancer; APOE is the gene for apolipoprotein E; FAD3 and XAD are hypothetical genes for familial Alzheimer’s dementia; APOB is the gene for apolipoprotein B; CETP is the gene for cholesteryl ester transfer protein; FCC4 is the hypothetical gene for familial colon cancer; APC is the gene for adenomatous polyposis coli; and NAT2 is the gene for *N*-acetyltransferase 2.*
A Hypothetical case in 2010

“John is pleased to learn that genetic testing does not always give bad news — his risks of contracting prostate cancer and Alzheimer’s disease are reduced, because he carries low-risk variants of the several genes known in 2010 to contribute to these illnesses. But John is sobered by the evidence of his increased risks of contracting coronary artery disease, colon cancer, and lung cancer”.

Collins F. Shattuck Lecture — Medical and societal consequences of the human genome project. NEJM 1999; 341: 28-37.
A Hypothetical case in 2010

“By 2010, the field of pharmacogenomics has blossomed, and a prophylactic drug regimen based on the knowledge of John’s personal genetic data can be precisely prescribed to reduce his cholesterol level and the risk of coronary artery disease to normal levels”.

Collins F. Shattuck Lecture — Medical and societal consequences of the human genome project. NEJM 1999; 341: 28-37.
PPPP (P) Medicine?

Predictive
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Do epidemiology and related population-based sciences suggest constraints on what can be done?
Mis-specifying individual risk of IHD: what to do?

“.. within any risk group, prediction is poor; it is not at present possible to express individual risk more precisely than as about a 1 in 6 chance of a hitherto healthy man developing clinical IHD in the next 5 years if he is at high risk” .... “There is a pressing need for prospective observational studies in which new risk factors are identified”

Meade TW, Chakrabarti R. Arterial disease research: observation or intervention? Lancet 1972;ii:913-6
From: Davey Smith G. Epidemiology, epigenetics and the “gloomy prospect”. Int J Epidemiol 2011;40:537-562
Johannes Heester .....
Johannes Heester quits smoking at age 106

"I did it for love, for my wonderful wife ... she should have me as long as possible..."
Chapter 2. Measurement and design for life course studies of individual differences and development, Jane Costello and Adrian Angold
Personalized medicine? Treatment responses of 20 participants on the same antidepressant in GENDEP

Uher R. Genes, environment and individual differences to responding to treatment for depression. Harv Rev Psychiatry 2011;19:109-24
“to revolutionise the treatment of depression ... [and] ... to make it easier for doctors to decide which antidepressant will be most likely to work for a given depressed person”

Peter McGuffin.

http://gendep.iop.kcl.ac.uk/background.php
Aridhia Informatics Ltd and Glencoe Software have formed a strategic partnership to create innovative products to aid the development of personalised therapies and deliver improved patient outcomes.

Professor Andrew Morris, Director of the Medical Research Institute at the University of Dundee, and co-founder of Aridhia Informatics said: This partnership brings together complementary strengths needed to accelerate the innovation of stratified “or personalised” medicines. Our vision is to become a world leader in providing the clinical and scientific information required for the personalised, targeted drugs and treatments of the future. The UK is a good place to do this work because of the opportunities for open innovation between NHS, academic and commercial partners.
Anyone who believes that the same thing can be suited to everyone is a great fool, since medicine is practiced not on mankind in general, but on every individual in particular.

Henri de Mondeville, circa 1250

quoted by Skrabanek P.
The death of humane medicine. London: The Social Affairs Unit; 1994
In statistical matters, when attempting to appreciate facts numerically, the first concern above all is to leave the individual out of sight by considering a man merely as a fraction of the species. One must deprive him of his individuality in order to eliminate whatever such individuality could accidentally introduce into the question.

In applied medicine, on the contrary, the problem is always individual, the facts which contribute to solve it present one by one; it is exclusively the personality of the patient with which we deal, and in the end it is a single human being with all his idiosyncracies that the doctor must treat. For us the masses remain entirely out of the question.

A great surgeon performs operations for stone by a single method; later he makes a statistical summary of deaths and recoveries, and he concludes from these statistics that the mortality law for this operation is two out of five. Well, I say that this ratio means literally nothing scientifically and gives us no certainty in performing the next operation; for we do not know whether the next case will be among the recoveries or the deaths.

Claude Bernard, *An Introduction to the Study of Experimental Medicine*, 1865
I've found the man for George's hernia.
In the patient who succumbed, the cause of death was evidently something which was not found in the patient who recovered; this something we must determine, and then we can act on the phenomena or recognize and foresee them accurately … What a physician needs to know is whether his patient will recover, and only the search for scientific determinism may lead to this knowledge.

Claude Bernard, *An Introduction to the Study of Experimental Medicine*, 1865
“In a given state of society, a certain number of persons must put an end to their own life. This is the general law; and the special question as to who shall commit the crime depends of course upon special laws; which, however, in their action, must obey the large social law to which they are all subordinate. And the power of the larger law is so irresistible, that neither love of life nor the fear of another world can avail anything towards even checking its operation”.

Henry Thomas Buckle, 1857
The limits of prediction
Why are children in the same family so different from one another?
Why are children in the same family so different from one another?

• Genetics apart, siblings are no more similar than two randomly selected individuals from the population they are from.

• They share many of the things that lifecourse epidemiologists have been interested in....

Plomin and Daniels, Behavioral and Brain Sciences, 1987 (IJE 2011)
What accounts for differences in health and other outcomes?

Partition of variance in twin studies (and other family based studies including adoption studies) into genetic contribution, shared environmental contribution (i.e. shared between people brought up in the same home environment and making members of the same family more similar) and non-shared environmental contribution.
What accounts for differences in health and other outcomes?

Partition of variance in twin studies (and other family based studies including adoption studies) into genetic contribution, shared environmental contribution (i.e. shared between people brought up in the same home environment and making members of the same family more similar) and non-shared environmental contribution.

Such studies generally generate zero or small estimates of the influence of shared environment.
Are the estimates wrong?

- Different study designs – conventional twin studies, separated twin studies, adoption studies, pseudo-randomised adoption studies and extended pedigree studies generally come to similar conclusions.

- They can all be biased – but the biases would be different.
Categories of “environmental” factors that cause children in the same family to differ

• Measurement error (non-shared environment is from subtraction)

• “Non-systematic non-shared environment” – stochastic processes during development and beyond

Plomin and Daniels, Behavioral and Brain Sciences, 1987 (IJE 2011)
Categories of “environmental” factors that cause children in the same family to differ

- **Systematic non-shared environment**
  - birth order, gender differences
  - sibling interaction
  - parental treatment
  - extrafamilial networks: peer groups, teachers, television

Plomin and Daniels, Behavioral and Brain Sciences, 1987 (IJE 2011)
The gloomy prospect

“What is happening environmentally to make children in the same family so different from one another? One gloomy prospect is that the salient environment might be unsystematic, idiosyncratic, or serendipitous events, such as accidents, illnesses, and other traumas, as biographies often attest”

Plomin and Daniels, Behavioral and Brain Sciences, 1987 (IJE 2011)
The voyage of the *Beagle* has been by far the most important event in my life, and has determined my whole career; yet it depended on so small a circumstance as my uncle offering to drive me thirty miles to Shrewsbury, which few uncles would have done, and on such a trifle as the shape of my nose.
“life’s single lesson: that there is more accident to it than a man can ever admit to in a lifetime and stay sane”

V, Thomas Pynchon, 1964
The gloomy prospect

“It is possible that nonshared environmental influences could be unsystematic in the sense of stochastic events that, when compounded over time, make children in the same family different in unpredictable ways. Such capricious events, however, are likely to prove a dead end for research. More interesting heuristically are possible systematic sources of differences within families”

Plomin and Daniels, Behavioral and Brain Sciences, 1987
Shared environment: a meaningful concept?

- Shared environment in childhood: declining effects on outcomes such as obesity
- Shared environment in adulthood – extended pedigree studies; spousal studies
- Face validity of estimates – e.g. music lessons vs playing in adulthood; child being read to but not reading on their own (Vinkhuyzen et al 2010)
Figure 5  Correlations on the Liberalism-Conservatism Index for MZ and DZ Twin Pairs by Age Cohort

Note: MZ pairs and DZ pairs are pooled across sex.

Source: Longitudinal study of adolescent twins (ages 9.5-17) combined with sample of adult twins (ages 18-88).
Reasons for under-estimating shared environment

• Low shared environment not true for all outcomes – e.g. antisocial behaviour, criminality, musical ability, lung function in adults

• Imprecisely estimated, wide confidence intervals overlapping with the null – which many models fix as zero

• Limited range of shared environments in study samples; sample attrition
Reasons for over-estimating or over-interpreting non-shared environment

• Failure to model gene-environment interactions (GxE); though gene-environment correlations (rGE) can deflate non-shared environmental influences
• Measurement error categorised as non-shared
• Failure to understand “objective” vs “effective” environments and the non-shared aspects of the shared environment
## Effects of heritable and environmental factors in cancers at various sites. Proportion of variance (95% CI)

<table>
<thead>
<tr>
<th>Site or type</th>
<th>Heritable factors</th>
<th>Shared environment</th>
<th>Non-shared environment</th>
</tr>
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<tbody>
<tr>
<td>Stomach</td>
<td>0.28 (0-0.51)</td>
<td>0.10 (0-0.34)</td>
<td>0.62 (0.49-0.76)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>0.35 (0.10-0.48)</td>
<td>0.05 (0-0.23)</td>
<td>0.60 (0.52-0.70)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.36 (0-0.53)</td>
<td>0 (0-0.35)</td>
<td>0.64 (0.47-0.86)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.26 (0-0.49)</td>
<td>0.12 (0-0.34)</td>
<td>0.62 (0.51-0.73)</td>
</tr>
<tr>
<td>Breast</td>
<td>0.27 (0.04-0.41)</td>
<td>0.06 (0-0.22)</td>
<td>0.67 (0.59-0.76)</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>0 (0-0.42)</td>
<td>0.20 (0-0.35)</td>
<td>0.80 (0.57-0.97)</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>0 (0-0.35)</td>
<td>0.17 (0-0.31)</td>
<td>0.82 (0.64-0.98)</td>
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<tr>
<td>Ovary</td>
<td>0.22 (0-0.41)</td>
<td>0 (0-0.24)</td>
<td>0.78 (0.59-0.99)</td>
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<td>Prostate</td>
<td>0.42 (0.29-0.50)</td>
<td>0 (0-0.09)</td>
<td>0.58 (0.50-0.67)</td>
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<td>Leukemia</td>
<td>0.21 (0-0.54)</td>
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Nonshared Environment: A Theoretical, Methodological, and Quantitative Review

Eric Turkheimer and Mary Waldron
University of Virginia

When genetic similarity is controlled, siblings often appear no more alike than individuals selected at random from the population. Since R. Plomin and D. Daniels' seminal 1987 review, it has become widely accepted that the source of this dissimilarity is a variance component called nonshared environment. The authors review the conceptual foundations of nonshared environment, with emphasis on distinctions between components of environmental variance and causal properties of environmental events and between the effective and objective aspects of the environment. A statistical model of shared and nonshared environmental variables is developed. A quantitative review shows that measured nonshared environmental variables do not account for a substantial portion of the nonshared variability posited by biometric studies of behavior. Other explanations of the preponderance of nonshared environmental variability are suggested.

Why Are Children in the Same Family So Different?

In what may have been the most influential article ever written in the field of developmental behavior genetics, Plomin and Daniels (1987) reviewed evidence that a substantial portion of the variability in behavioral outcomes could not be explained by the additive effects of genotype or the environmental influences of gate the origins of nonshared environmental variance. The following is typical:

Research on nonshared environment can be categorized into (a) analyses of the magnitude of the nonshared environment component of variance, (b) attempts to identify specific nonshared factors that are experienced differently by siblings in a family, and (c) explorations of
Variation of growth of genetically identical marbelled crayfish in an aquarium

How well would epidemiologists be able to predict outcome?

A third component causing random variability beside environment and genotype. A reason for the limited success of a 30 year long effort to standardize laboratory animals?

KLAUS GÄRTNER

Medizinische Hochschule Hannover, Abt. Versuchstierkunde Konstanty-Gutschow-Str. 8, D-3000 Hannover, Federal Republic of Germany

Summary
This paper is a review of experiments, performed in our laboratory during the past 20 years, designed to analyse the significance of different components of random variability in quantitative traits in laboratory rats and mice. Reduction of genetic variability by using inbred strains and than the consequence of heterogeneous environmental influences. In a group of inbred rats, the males with the highest chance of parenting the next generation were gathered in the central classes of the distribution of the body weight.

Keywords: Components of variance of body
Sewall Wright holding a guinea pig in each hand circa 1920.
Random phenotypic variance? Piebald pattern in guinea pigs

Sewall Wright 1921
58% of the variance intangible ..

“differences .. must be due to irregularities in development due to the intangible sort of causes to which the word chance is applied”

Sewall Wright 1921
Stochastic events at the level of gene expression and epigenetic processes

Waddington’s epigenetic landscape
Epigenetics: the confused epidemiologist's friend.

If they ask you anything you don't know, just say it's due to epigenetics.

Davey Smith G Int. J. Epidemiol. 2012;41:303-308
Could Nonshared Environmental Variance Have Evolved to Assure Diversification Through Randomness?

Edward M. Miller
Professor of Economics and Finance, University of New Orleans

The advantages of being random?

One of the more striking findings of modern human behavior genetics is the relatively small role for shared environmental experience and the large role for what is called non-
Chance from the subcellular to the biographical level

Chance at the ontological or epistemological level
whether an exposed subject does or does not develop a cancer is largely a matter of luck; bad luck if the several necessary changes all occur in the same stem cell when there are several thousand such cells at risk, good luck if they don’t. Personally I find that makes good sense, but many people apparently do not.

Richard Doll. Commentary on the age distribution of cancer. IJE 2004;33:1183-4
Winnie: the tail of a distribution or a black swan?
Smoking and lung cancer

- lung cancer in cohort studies, pseudo-variance explained 5-10% at best
- lung cancer trends in US, 93% of variance (Whittmore 1989)
- geographical differences within US virtually all variance (Weinberg 1982)
- between-country differences ditto
Lung cancer

• Heritable: 26%
• Shared environment 12%
• Non-shared environment 62%
• Most traits have a non-trivial heritable component – good news in that genetic variants can tell us about modifiable causes
• Exposures with apparently small contributions in terms of variance explained can account for most cases of disease in a population
• Unstable aspects of non-shared environment may account for high proportions of the variance but are intractable; luckily they will often not be confounders
• Modifiable exposures that the genetic and shared environmental components are informative about are likely to be the appropriate group-level public health targets
Personalized medicine? Treatment responses of 20 participants on the same antidepressant in GENDEP

Uher R. Genes, environment and individual differences to responding to treatment for depression. Harv Rev Psychiatry 2011;19:109-24
“to revolutionise the treatment of depression ... [and] ... to make it easier for doctors to decide which antidepressant will be most likely to work for a given depressed person”

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Good prediction of group-level risk with limited prediction of individual risk a common phenomenon

- Earthquakes
- Manhole cover explosions
Results from the Bronx blind prediction test. The axis is the predicted rank. Each arrow labelled “X” indicates a 2009 manhole explosion, and each arrow labelled “F” indicates a 2009 manhole fire.

Good prediction of group-level risk with limited prediction of individual risk a common phenomenon

- Earthquakes
- Manhole cover explosions
- Hit records
Why does a hit become a hit?

Good prediction of group-level risk with limited prediction of individual risk a common phenomenon

- Earthquakes
- Manhole cover explosions
- Hit records
- Promoting staff
- Choosing a partner
A Hypothetical case in 2010

“John, a 23-year-old college graduate, is referred to his physician because a serum cholesterol level of 255 mg per deciliter was detected in the course of a medical examination required for employment. He is in good health but has smoked one pack of cigarettes per day for six years….. To obtain more precise information about his risks of contracting coronary artery disease and other illnesses in the future, John agrees to consider a battery of genetic tests that are available in 2010”.

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Results of genetic testing in a hypothetical patient in 2010 (from Collins, 1999) and updated estimates of relative risks associated with common variants in these genes in brackets

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A hypothetical case in 2020..

“It's the “Year of Perfect Vision,” 2020. Amy, age 21 years, visits with her physician and elects to have complete genome sequencing. At a follow-up visit, Amy chooses to learn of her genetic risk factors for heart disease, diabetes, breast cancer, and colon cancer”.

Percentage of individuals in the general population who would test positive by whole-genome sequencing.

The fraction of cases (i.e., patients with disease) who would test positive by whole-genome sequencing

Roberts NJ. The predictive capacity of personal genome sequencing.
Science Translational Medicine 2012; doi: 10.1126/scitranslmed.3003380
Relative risk of disease in individuals testing negative by whole-genome sequencing.

Mis-specifying individual risk of IHD: what to do?

“.. within any risk group, prediction is poor; it is not at present possible to express individual risk more precisely than as about a 1 in 6 chance of a hitherto healthy man developing clinical IHD in the next 5 years if he is at high risk” .... “There is a pressing need for prospective observational studies in which new risk factors are identified”

Meade TW, Chakrabarti R. Arterial disease research: observation or intervention? Lancet 1972;ii:913-6
‘It has long been a commonplace observation in the discipline of social anthropology that cultural systems of explanation or accountability [for the occurrence of a misfortune] need to address two distinct issues. In the first place the general kind of misfortune: how and why does it happen? In the second place, the site and time of particular misfortune require explanation: how and why did it happen to this person at this time? ... In our own society, where the development of science has shaped so many other cultural institutions, it is sometimes overlooked that this pair of explanations is still required. This is so because it is a central pillar of the Western scientific tradition that the two explanatory systems are unified.’

“For more than one hundred years it has been recognized that digitalis had a beneficial action in certain forms of heart disease, but no definite knowledge existed as to the kind of heart disease which benefited, so that every person supposed to have a heart affection was given digitalis. Careful investigation has revealed that the drug is of use in only a small percentage of cases, and that of a particular kind. We can now recognize with fair certainty the cases where it will have a good effect and those cases in which it is of no use”.

Mackenzie J. The opportunities of the general practitioner are essential for the investigation of disease and the progress of medicine. BMJ 1921; 797–804. Reprinted IJE.
Increased mortality among patients taking digoxin-analysis from the AFFIRM study


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Aims

Digoxin is frequently used for rate control of atrial fibrillation (AF). It has, however, been associated with increased mortality. It remains unclear whether digoxin itself is responsible for the increased mortality (toxic drug effect) or whether it is prescribed to sicker patients with inherently higher mortality due to comorbidities. The goal of our study was to determine the relationship between digoxin and mortality in patients with AF.

Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial

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Aims

Digoxin is recommended for long-term rate control in paroxysmal, persistent, and permanent atrial fibrillation (AF). While some analyses suggest an association of digoxin with a higher mortality in AF, the intrinsic nature of this association has not been examined in propensity-matched cohorts, which is the objective of the current study.
Although Mackenzie placed the emphasis in terms of record-keeping in the Institute on its research purpose, his interest was … not an epidemiological one - he was not concerned with disease in populations. He was concerned with the mechanism of disease in the individual and how the early symptoms and signs of disease were related to developing pathology.

MacNaughton J. The St Andrews Institute for Clinical Research: An Early Experiment in Collaboration. Medical History 2002;46:549-568
Alex Mair reporting on interviews with Mackenzie’s cousin, the socialist general practitioner and researcher Andrew Garvie (1885-1969).

“How could a heterogeneous group of general practitioners collect masses of recorded signs and symptoms, unless and until some means could be found to handle group data. The observations of one man important in a different age, had now to be sacrificed for a different technique which we now realise as the epidemiological method…. Beyond a certain limit, large numbers of symptoms, physical signs, social, psychological and environmental data relating to many patients could only be handled successfully by resort to a different and more impersonal method of numerical analysis… Some future Mackenzie Lecturer might well find it profitable to give further study to the relationship between these two men, and to ascertain to what extent Garvie formed the bridge between two distinct eras in general practice, the one clinical research and the other epidemiology”.

Newman is preparing to dash on the same rock. This scheme of his to keep records of people before they are born till their death, is bound to fail for reasons so obvious that I can only conclude he his wilfully shutting his eyes to the danger.

Mackenzie to Walter Morley Fletcher. March 29th 1920.

PPPP (P) Medicine?

Predictive
Preventive
Personalized
Participatory
(Population perspective)


PPPP (P) Medicine and common complex disease?

There are epistemological limits to the degree of prediction

By far the best predictor is existing disease (which somewhat vitiates the purpose of PPPP medicine)

For treatment post-event targeting has promise, currently most clearly in cancer

For prevention attempts at “personalisation” against a background of non-random under-treatment may be diversionary
The true observer is he who is content to do the spade-work, indifferent as to who shall realise the result, so long as the aim of Medicine is achieved.

James Mackenzie