The Academy of Medical Sciences

Stratified Medicine Stakeholder meeting

Informatics

The Farr Institute: Establishment and Programme of work

Professor Iain Buchan
Professor of Public Health Informatics and Director of the Centre for Health Informatics, University of Manchester
Director of the Health e-Research Centre, Farr Institute

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Informatics for Stratified Medicine

From endotype discovery to adaptive personalisation

Iain Buchan

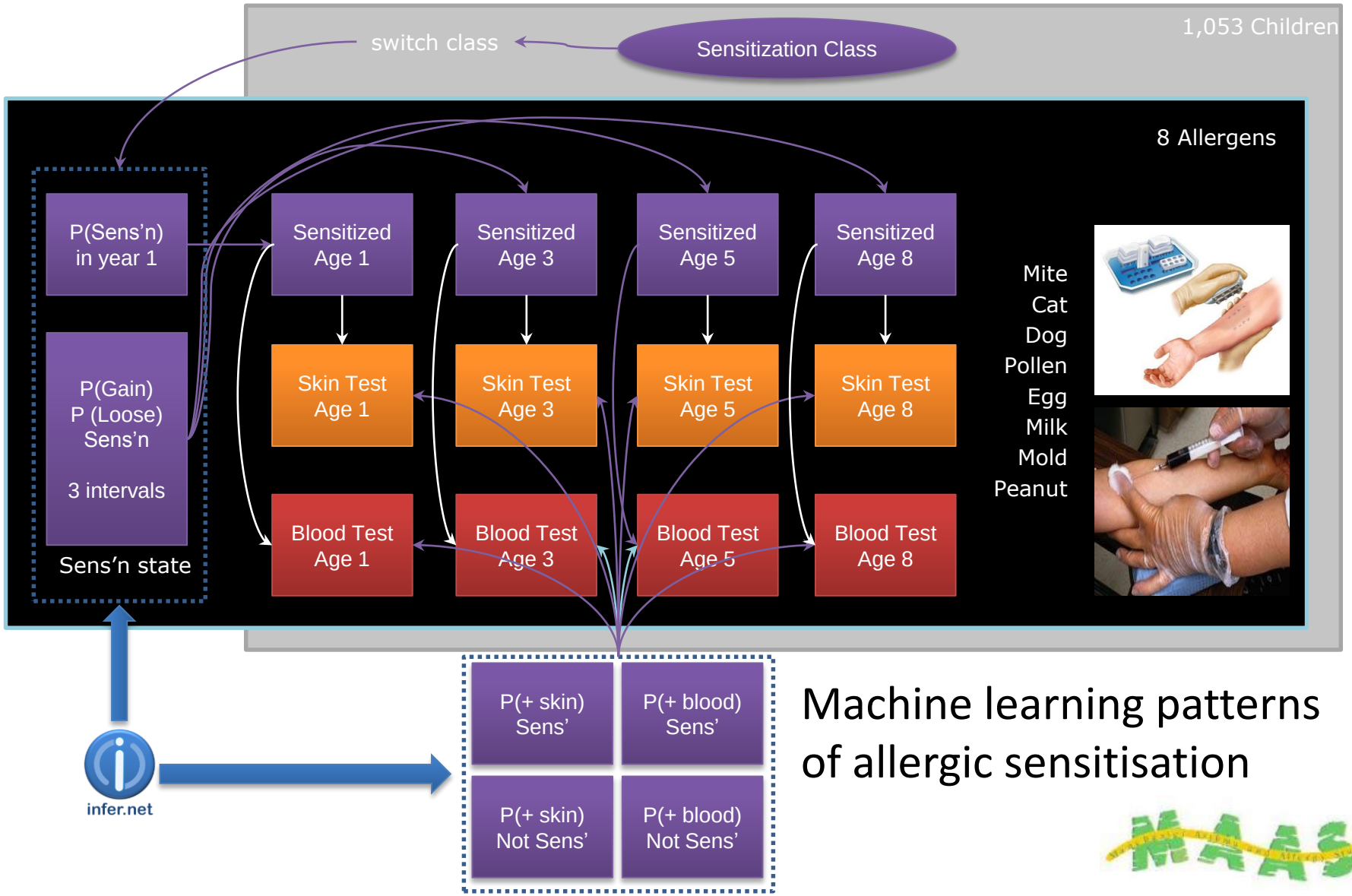
Director, Health e-Research Centre (HeRC), Farr Institute

Stratified Medicine Stakeholder Meeting

Academy of Medical Sciences

8th November 2013

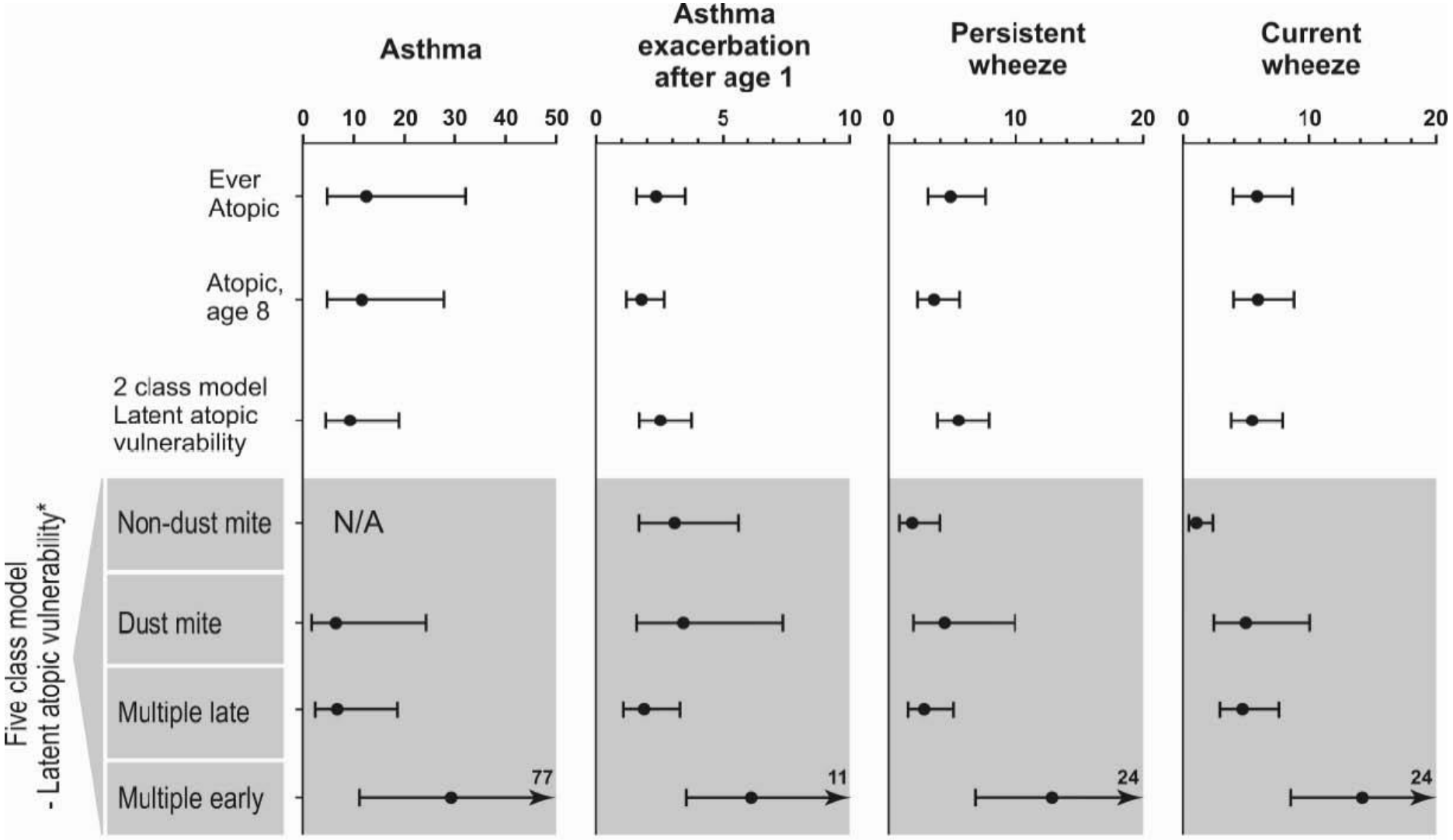
Machine-learned Phenotypes



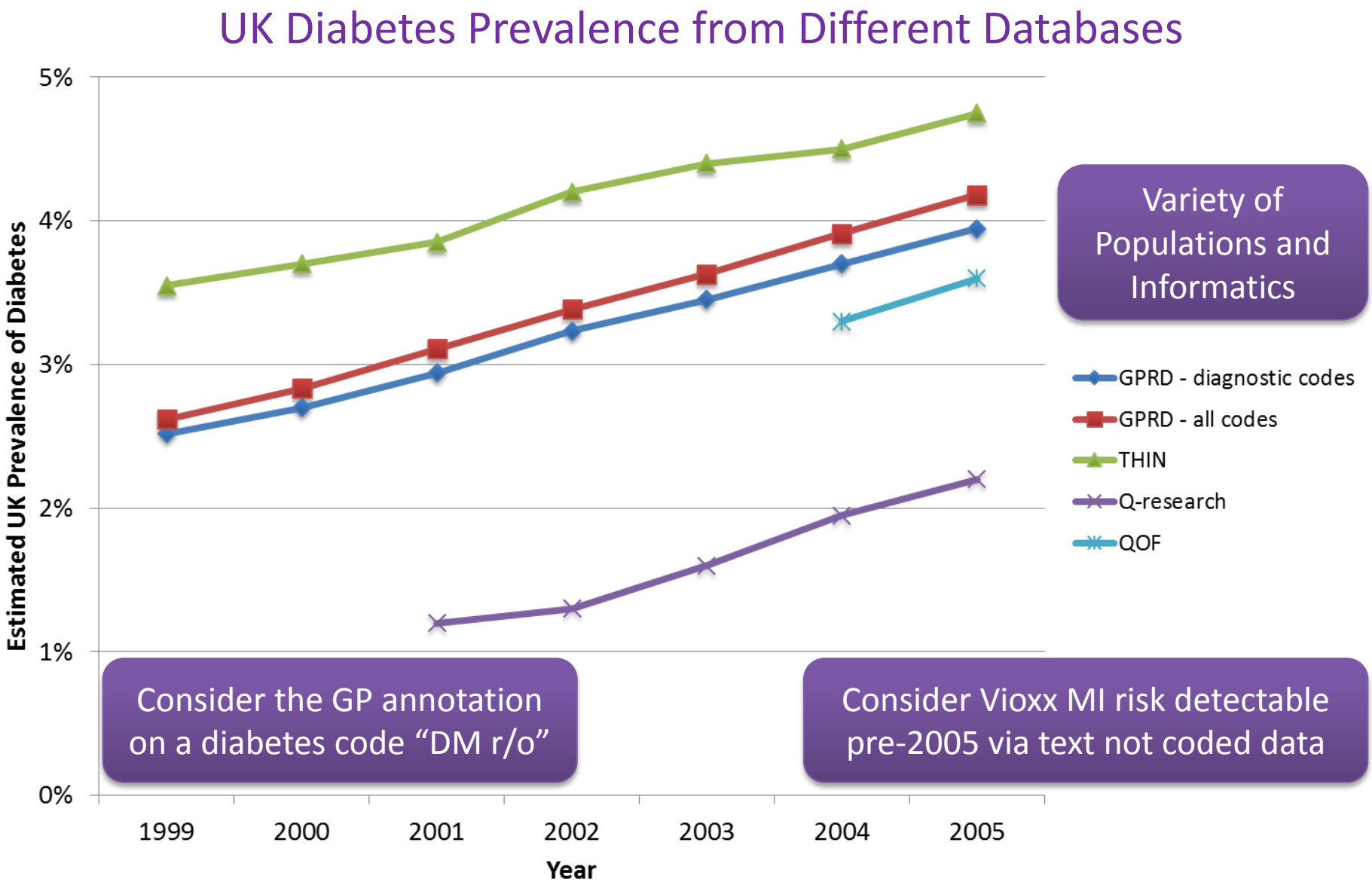
Machine learning patterns of allergic sensitisation

Atopy 'Stratified'

Unanticipated risk group for asthma discovered



Phenotypes from Care Data



From E. Kontopantelis & T. Doran

Toward Sense-making Networks

Different uses of healthcare care data borrowing strength from one another and engaging 'linkable' experts

Clinical Trial:
1 vs. 2 per day dosing → adherence (* deprivation)

Salford Lung Study

Clinical Audit:
Depression vs. readmission

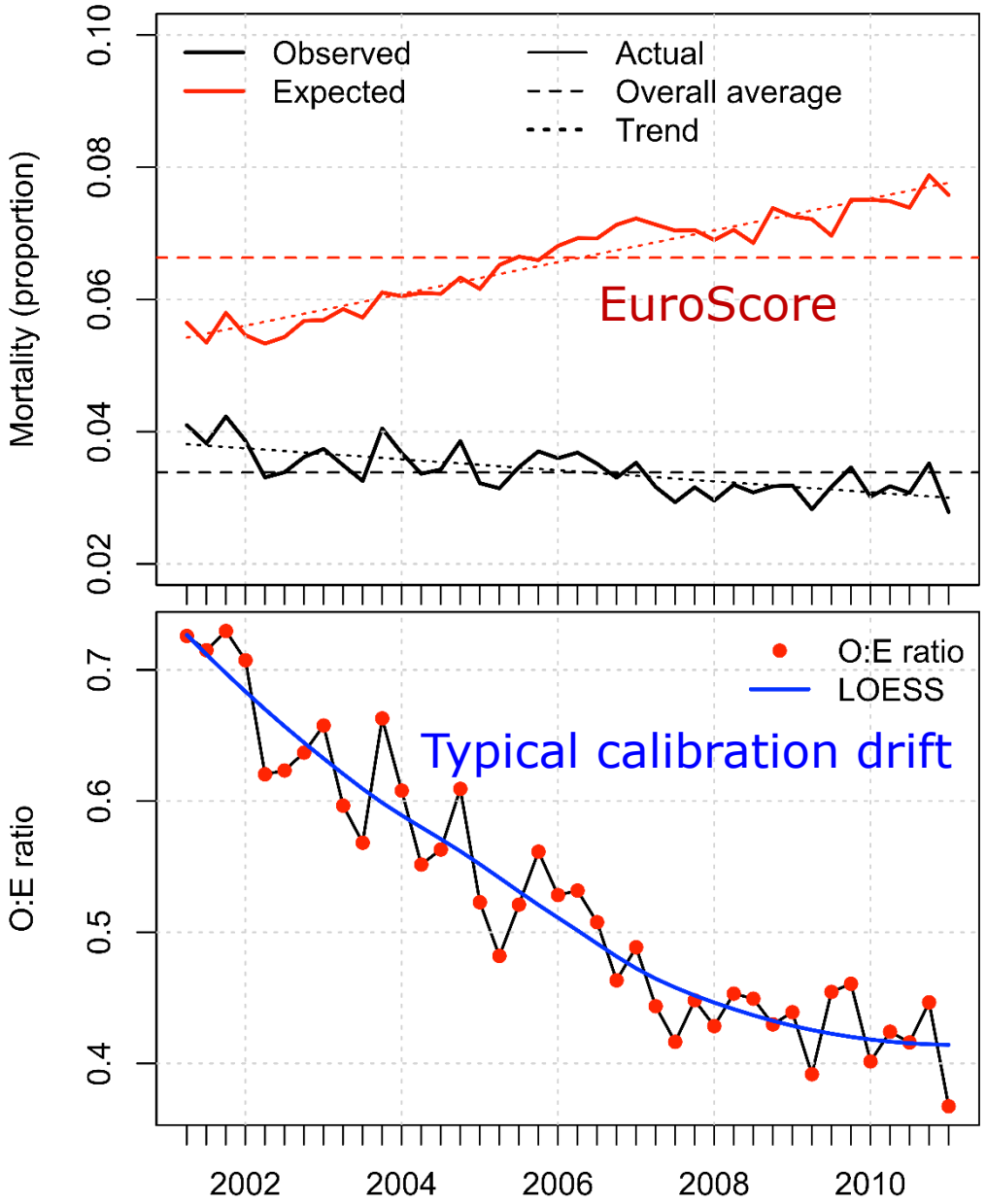
Salford Royal NHS
NHS Foundation Trust

Public Health:
Recalibrated deprivation score

Salford City Council

"Users who selected the variables in your basket also selected these variables and these models…"

Algorithms as Medical Devices?



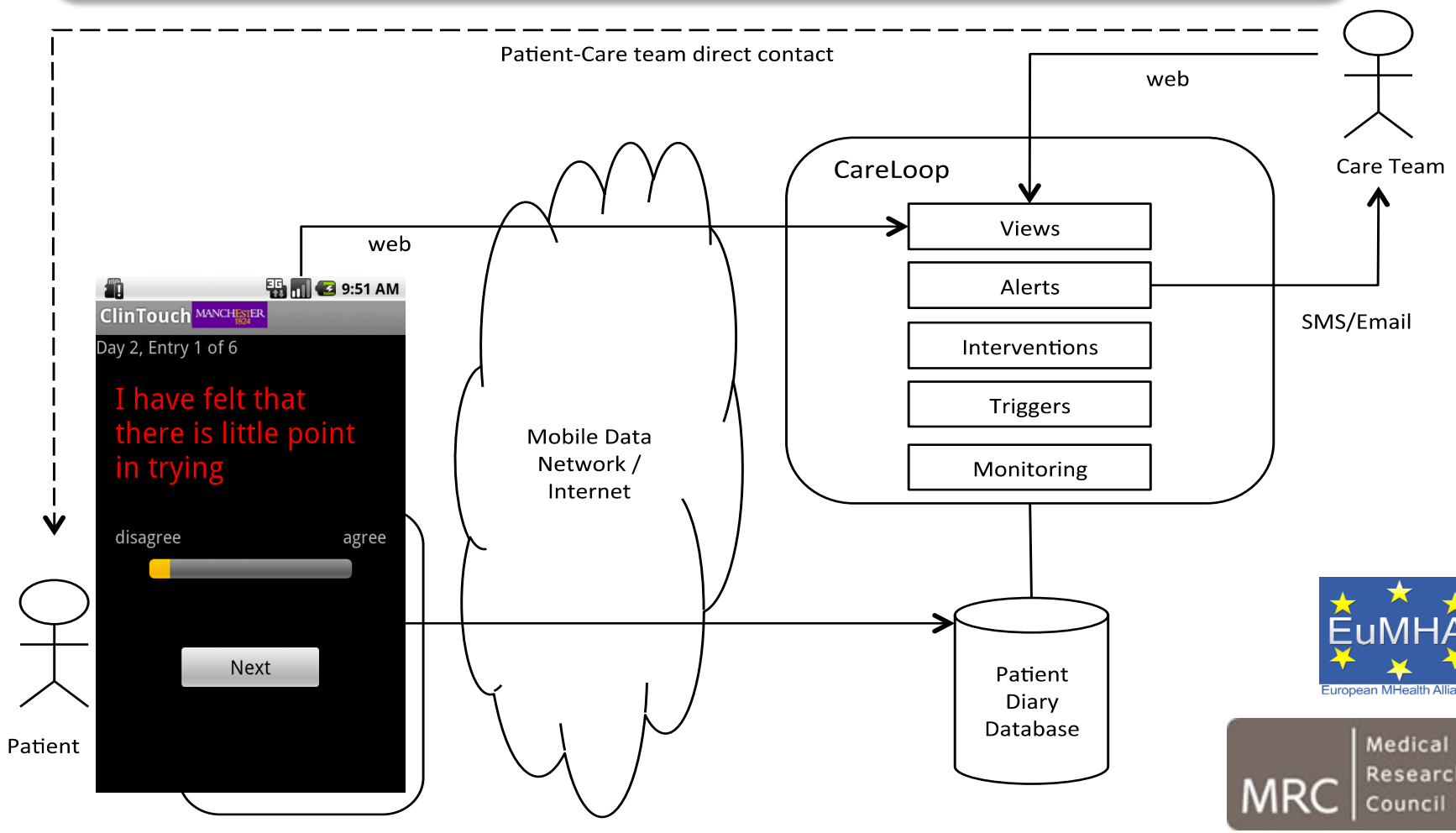
Production line of clinical prediction models is broken

EU Directive 2007/47:
The law now sees algorithms as medical devices

From G. Hickey & B. Bridgewater

Patient + Mobile = n-of-1 Frontier

Reducing Relapse in Schizophrenia via Smartphone
Drug + behaviour (information * psychological endotype) = outcome



EuMHA
European MHealth Alliance

MRC Medical Research Council

From J. Ainsworth & S. Lewis

Big Data Climate for Healthcare

DATA

Vast data volume, velocity, variety

TSUNAMI

METHODS & MODELS

Supra-linear growth in papers & tools

BLIZZARD

EXPERTISE

Similar number of analysts

DROUGHT

<u>Incubating the UK's Experts: Status Quo</u>

Islands of: Bioinformatics; Health Informatics; Disease/Mechanism-specific Research

NHS IT Staff (NW, 5k): <8% Postgraduate Qualification; <18% Degree

Farr: Seeding UK-Scale Health Informatics

- Capacity
  - Leaders: PhDs & Annual Scientific Meeting
  - 'Babel fish': MSc; CPD & Professionalization
- Methods
  - Data Science (Stats & Engineering 'reactor')
  - Linked phenotyping 'machines': safe havens
- Demonstrators
  - Public good (science ↔ service-development)
  - UK Health data 'LHC' (data, methods, experts)

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Regulation

Influencing the European *in vitro* Diagnostic Medical Devices Regulation

Mr Graeme Tunbridge

Head of Medical Devices EU Policy, Medicines and Healthcare products Regulatory Agency

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Regulation

Accreditation and quality assessment of laboratories developing and performing ‘in-house’ tests

Dr Rachel Butler

Chair of the UK National External Quality Assessment Service’s Special Advisory Group for Molecular Pathology

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Accreditation and Quality Assessment of laboratories developing and performing “In-house tests”

Rachel Butler

Head of All Wales Genetics Laboratory

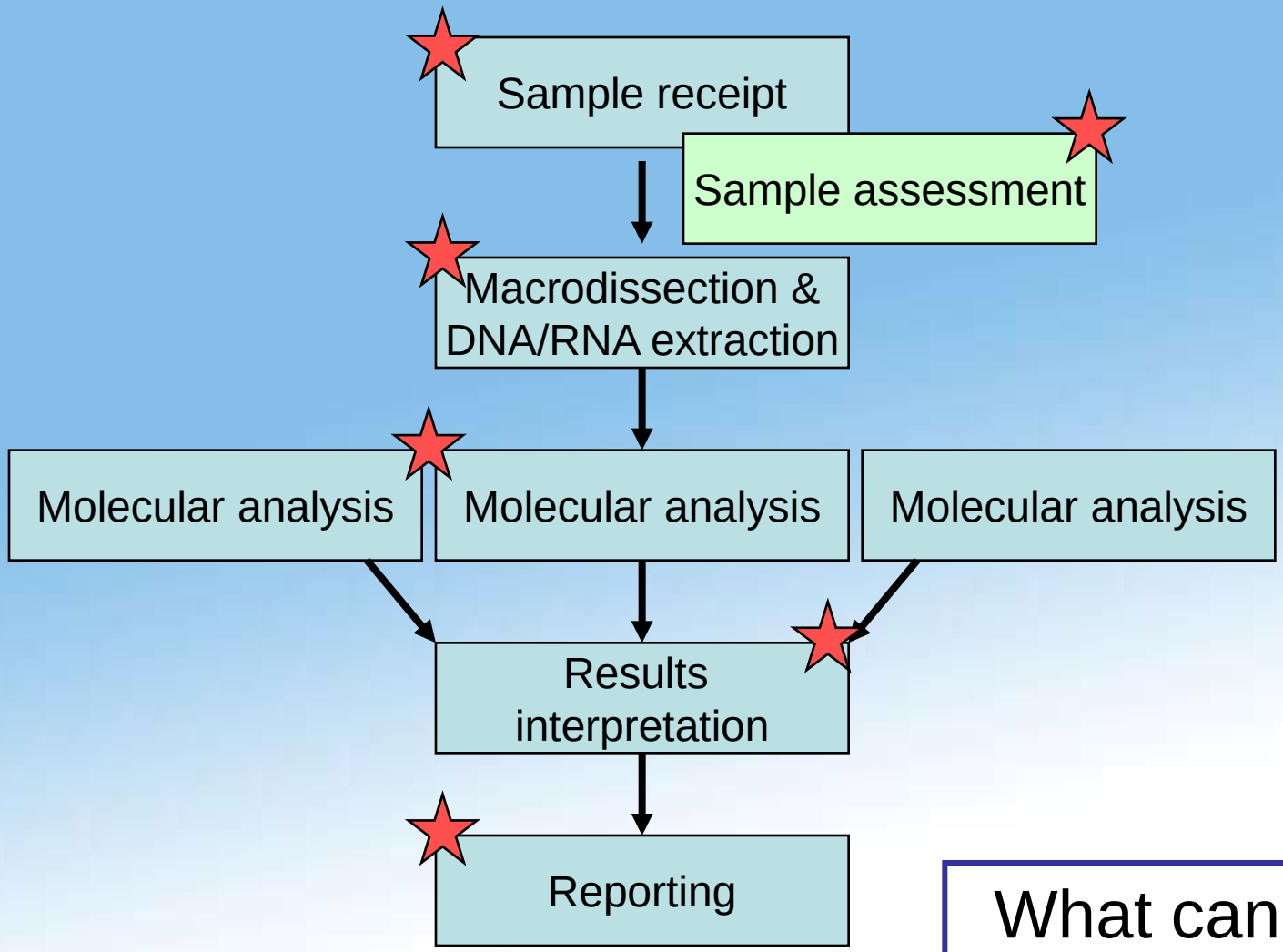
(provider of strat med services and clinical trials since 2008)

Technology Hub, CR-UK SMP

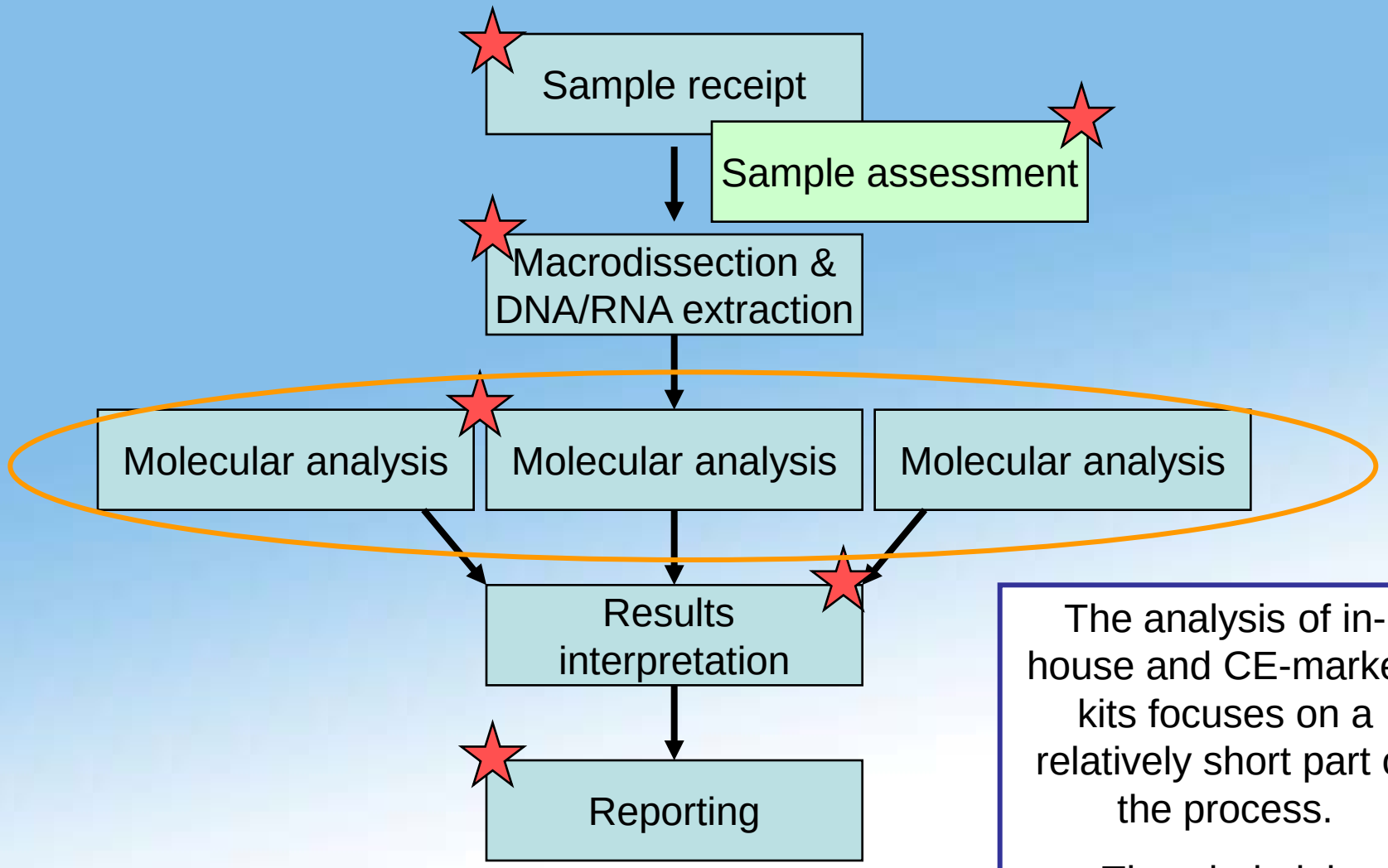
Chair, UK NEQAS SAG for Molecular Pathology

Genetics rep, RCPath Interspecialties committee on Molecular Pathology

NHS WALES GIG CYMRU | All Wales Medical Genetics Service



What can, and does go wrong?



The analysis of in-house and CE-marked kits focuses on a relatively short part of the process.

The whole lab operation needs to be assured for high quality services.

ISO 15189

Lab accreditation

- **Organisation**

  – robust, financially sound, correct reporting arrangements
- **Personnel**

  – appropriately directed, qualified workforce, CPD, ongoing competence, PADR, training records
- **Environment**

  – equipment purchase & maintenance, temperature monitoring, security, storage of clinical records and samples, H&S, chemicals & reagents
- **Quality**

  – Auditing (horizontal and vertical), incident reporting, quality management system, improvement process, QM, responsive to users requirements, **EQA participation**

ISO 15189

Lab accreditation

CPA

Analytical processes (in-house or kit)

- Selection of appropriate technology
- (Protocol development / optimisation)
- Staff training and competence sign-off
- Validation (repeated for every change to protocol)
  - Positive, negative and blank controls
  - Controlled documents stored in QMS
- Reagents batch tested
- Controlled SOP – changes acknowledged by all holders
- Witnessed tube transfers
- Results independently interpreted by 2 competent staff

ISO 15189

Lab accreditation

CPA

Analytical processes (in-house or kit)

- Selection of appropriate technology
- (Protocol development / optimisation)
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- Val
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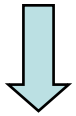
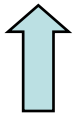
- Wit
- Results independently interpreted by 2 competent staff

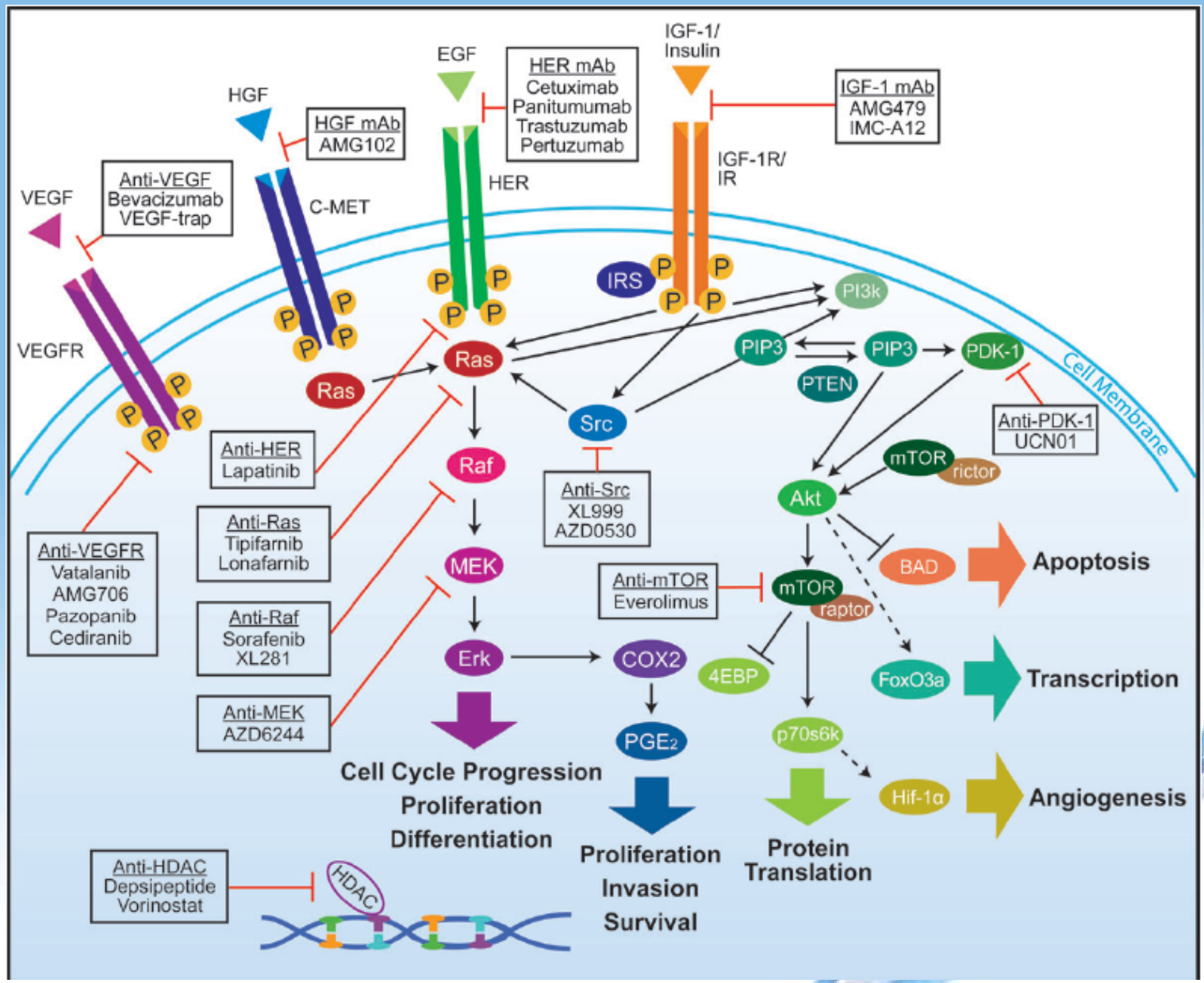
Genetic labs have used IHTs for majority of inherited disease services (out of necessity)

Virtually no poor performance in EQA

Virtually no adverse events reported (e.g. incorrect predictive, prenatal tests)

In-house tests and CE-marked kits

	In-house validated tests	**CE-marked kits**
Diagnostic lab adoption	Rapid response to new discoveries, clinical trial data (e.g. *KRAS, NRAS*)	Great workflow, generally good automation & simple analysis
Sensitivity and specificity	Comprehensive gene coverage and inclusion / characterisation of required mutations (e.g. *BRAF* p.V600K; *EGFR* p.L861Q)	Generally good sensitivity, but biased towards specific, known mutation sets
Cost	 e.g. *EGFR* tests. £190 using CE-kit or £120 using IHT. For 450 pa, difference of £31.5k for Welsh NHS 	
Trouble-shooting	Total access, scientists understand technology	Risk that users don't understand – inadequate access to raw data
Future flexibility	Potential to analyse the tumour biology and assay all potential druggable markers simultaneously (e.g. by NGS) – deliver required dx services.	Risk of one kit per NICE-approved drug


IGF-1/
Insulin
EGF
HER mAb
Cetuximab
Panitumumab
Trastuzumab
Pertuzumab
IGF-1 mAb
AMG479
IMC-A12
HGF
HGF mAb
AMG102
Anti-VEGF
Bevacizumab
VEGF-trap
VEGF
C-MET
HER
IGF-1R/
IR
VEGFR
IRS
PI3k
Ras
PIP3
PIP3
PDK-1
PTEN
Cell Membrane
Src
Anti-PDK-1
UCN01
Anti-HER
Lapatinib
Raf
mTOR
rictor
Akt
Anti-Src
XL999
AZD0530
Anti-Ras
Tipifarnib
Lonafarnib
Anti-VEGFR
Vatalanib
AMG706
Pazopanib
Cediranib
MEK
Anti-mTOR
Everolimus
mTOR
raptor
BAD
Apoptosis
Anti-Raf
Sorafenib
XL281
Erk
COX2
4EBP
FoxO3a
Transcription
Anti-MEK
AZD6244
PGE2
p70s6k
Hif-1α
Angiogenesis
Cell Cycle Progression
Proliferation
Differentiation
Proliferation
Invasion
Survival
Protein
Translation
Anti-HDAC
Depsipeptide
Vorinostat
HDAC

UK NEQAS Mol Path (2012-13, 2013-14)

Scheme		Error type		
Poor performers		Genotype	Sample swap	Interpretation
KRAS (mCRC) -run since 2008	CE-kit	5		4
	In-house	2	1	2
EGFR (NSCLC) -run since 2010	CE-kit	6	1	1
	In-house	10		1
BRAF (MM) -run since 2012	CE-kit	4	1	1
	In-house	1		

Full EQAs with RCPath NQAAP poor performance monitoring.

12 EQA samples assessed during this period

UK NEQAS Mol Path (2012-13, 2013-14)

Scheme		Error type		
Poor performers		Genotype	Sample swap	Interpretation
KRAS (mCRC) -run since 2	CE-kit	5		4
EGFR (NSC -run since 2				
BRAF (MM) -run since 2012	CE-kit	4	1	1
	In-house	1		

Errors: CE-kits > IHT (slight!!)

(My view) Due to the labs performing the tests and NOT the tests themselves ("Plug and play" culture)

Full EQAs with RCPath NQAAP poor performance monitoring.

12 EQA samples assessed during this period

Recommendations for providers
(KPI document in preparation – ACP)

- Accreditation with appropriate body
- Staff qualifications and training
- (Successful) EQA participation
- Service repertoire (workload breadth & depth)
- Meeting required turnaround times
- Assay sensitivity
- Assay failure rate
- Audit of mutation detection rates (within expected range)
- Test validation and documentation
- Service user feedback

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Stratified Medicine Stakeholder meeting

Pricing and Reimbursement

Introducing a system of flexible pricing based on value

Mr Danny Palnoch

Head of Medicines Analysis (Medicines, Pharmacy and Industry), Department of Health

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Department of Health

Stratified Medicines:

How They are Valued

Danny Palnoch
Senior Economic Adviser
Medicines, Pharmacy Industry
Department of Health

The Principle

- **The value of stratification can be readily assessed in terms of ‘harm avoided’.**
  - Ability to treat the patients who do not respond to the new drug with an alternative if the stratification is able to identify them in advance of the treatment – a net health gain.
  - Ability to avoid side-effects in the non-responder group – a net health gain.
- This health gain (the avoided health loss) can readily be assessed, using standard cost/effectiveness analysis, which NICE undoubtedly would do, and any other HTA bodies following standard methods would do too.

Example 1: With comparator

Pre-stratification

- New drug treats 200 patients. It generates 5 QALYs in 100 of them, and none for the other 100 – but you don't know in advance which patients will benefit.
- There is a comparator, which generates 1 QALY across all patients.

The incremental gain of the new drug is 300 QALYs across the whole treatment population, so at £25k/QALY, company can generate £7.5m of revenue.

Post-stratification

New drug treats only the 100 patients that benefit, generating 5 QALYs each.

Comparator generates 1 QALY over the same 100 patients.

The incremental gain of the new drug is 400 QALYs across the stratified population, so at £25k/QALY, company can generate £10m of revenue.

Example 1: with comparator

		QALY Gain	
	No. of patients	**Stratified Med**	**Comparator**
	Before stratification		
Group 1	100	0	1
Group 2	100	5	1
QALYs		500	200
Incremental QALY Gain			**300**
Revenue @ 25k/QALY			**£7,500,000**

Example 1: with comparator

		QALY Gain	
	No. of patients	**Stratified Med**	**Comparator**
	After stratification		
Group 1			
Group 2	**100**	**5**	**1**
QALYs		**500**	**100**
Incremental QALY Gain			**400**
Revenue @ 25k/QALY			**£10,000,000**

Example 2: With side effects

Pre-stratification

- New drug treats 200 patients, generating 4 QALYs in 100 of them, and, as the drug has side effects, generates -1 QALY in the other 100 patients, generating 300 QALYs in total. We do not know in advance who will benefit and who will have just the side effects.
- There is no comparator.

The incremental gain of the new drugs is 300 QALYs across the whole treatment population, so at £25k/QALY, company can generate £7.5m revenue.

Post-stratification

New drug treats only the 100 patients for whom the drug generates net health gain, a gain of 4 QALYs per patient, and no health loss.

The incremental gain from the new drug is 400 QALYs across the stratified treatment population, so at £25k/QALY, company can generate £10m of revenue.

Example 2: with side effects

	QALY Gain	
	No. of patients	Stratified Med
	Before stratification	
Group 1	100	-1
Group 2	100	4
QALYs		300
Incremental QALY Gain		300
Revenue @ 25k/QALY		£7,500,000

Example 2: with side effects

	QALY Gain	
	No. of patients	Stratified Med
	After stratification	
Group 1		
Group 2	100	4
QALYs		400
Incremental QALY Gain		400
Revenue @ 25k/QALY		£10,000,000

Flexible Pricing

- Unlike branded medicines, diagnostic devices have freedom of pricing. To the extent that the 'value added' relates to the diagnostic, the manufacturer can adjust the price at any point in time.
- Within the current PPRS, there are arrangements that can allow prices to change if the value assessment changes (within certain boundaries). The Heads of Agreement for the 2014 PPRS states:
- **"Subject to any agreed amendments the rules on flexible pricing will apply as now with companies given flexibility to increase or decrease the original list price only when significant new evidence is generated that changes the value of an existing indication or where a major new indication is proposed whose value to NHS patients is significantly different from the original indication. This will only apply when medicines are subject to NICE appraisal and a review by NICE will be required to determine whether the proposed revised price provides value to the NHS."**