Towards Genome Medicine: UK perspective

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Characterizing and Displaying Genetic Variants for Clinical Action Workshop

1st December 2011, Gaithersburg, US

Human Genome Sequence Costs

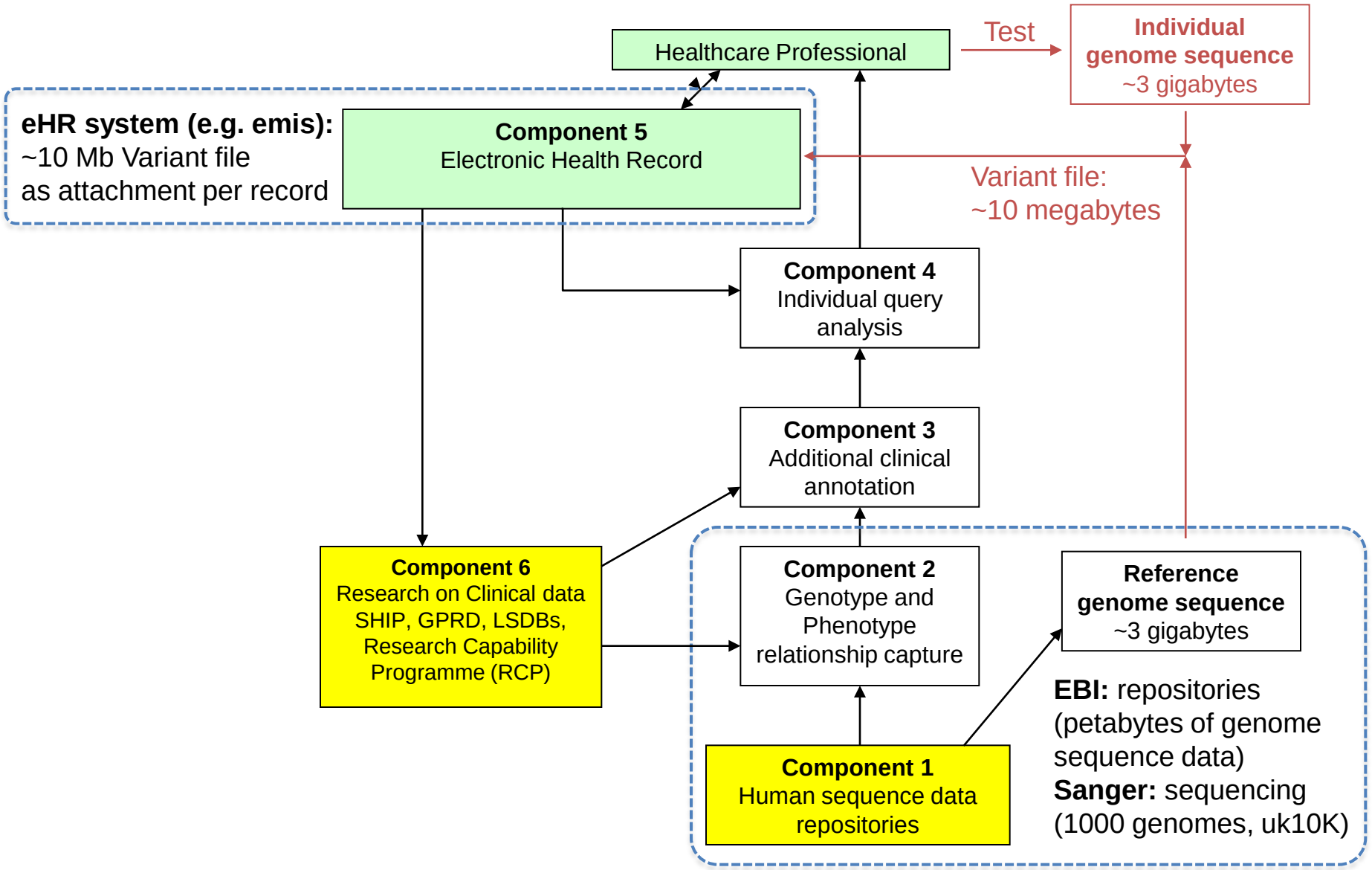
- Full genome sequence ~£5,000 [10/2011]
- Dropping in price 10x every 2-4 years
- Existing clinical genetic test ~£1,000 (UKGTN)

- Disk cost to store raw sequence ~£100
- Disk cost to store individuals variations ~10p

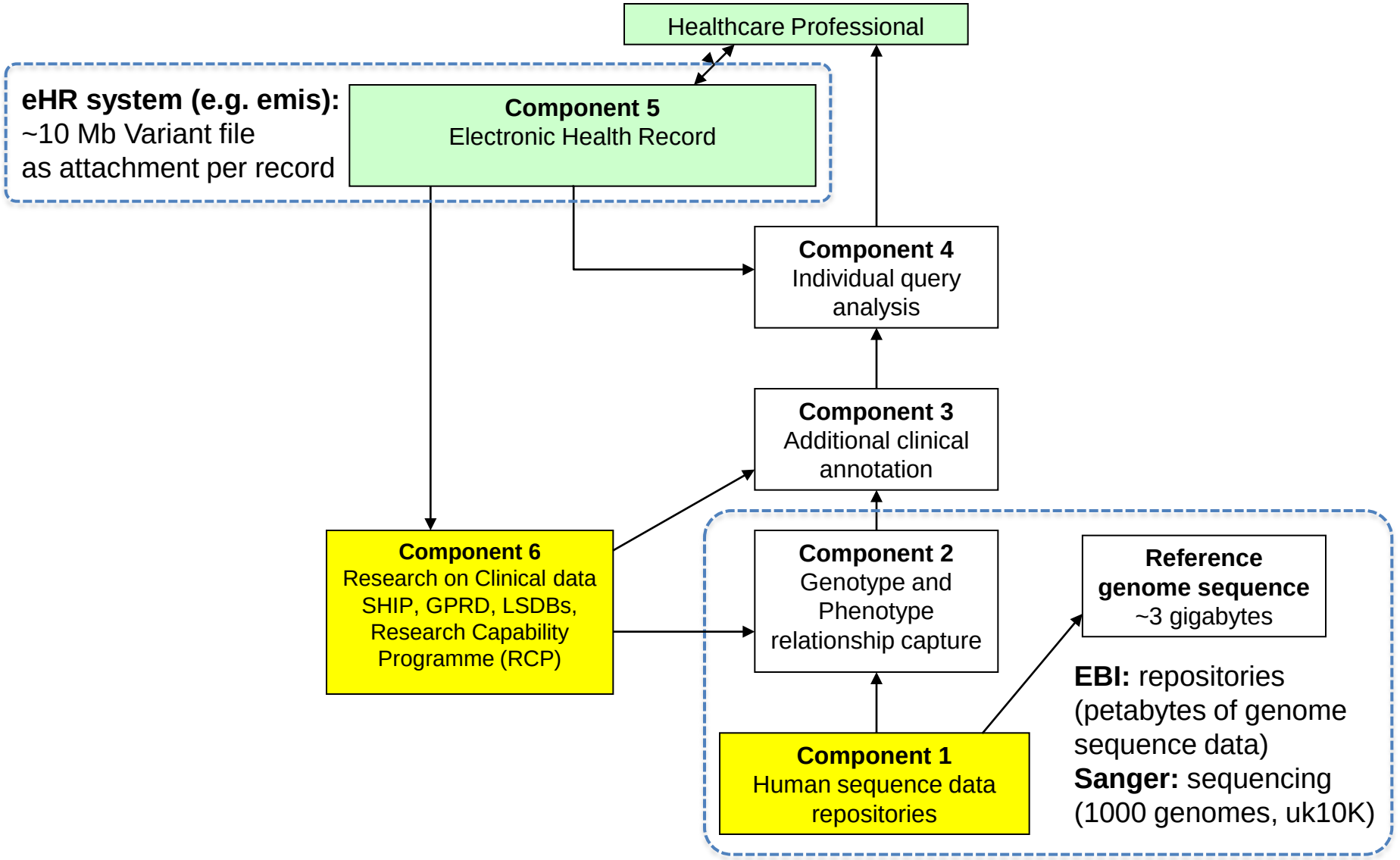
Towards Genomic Medicine in UK

- 2006 Creation of OSCHR (Office for Strategic coordination of Health Research) to increase coordination of MRC and NHS research
- 2007 Creation of OSCHR E-health board: enabling research over health records
- 2009 House of Lords report on Genomic Medicine
- 2010 Creation of UK Government Human Genomic Strategy Group (HGSG)

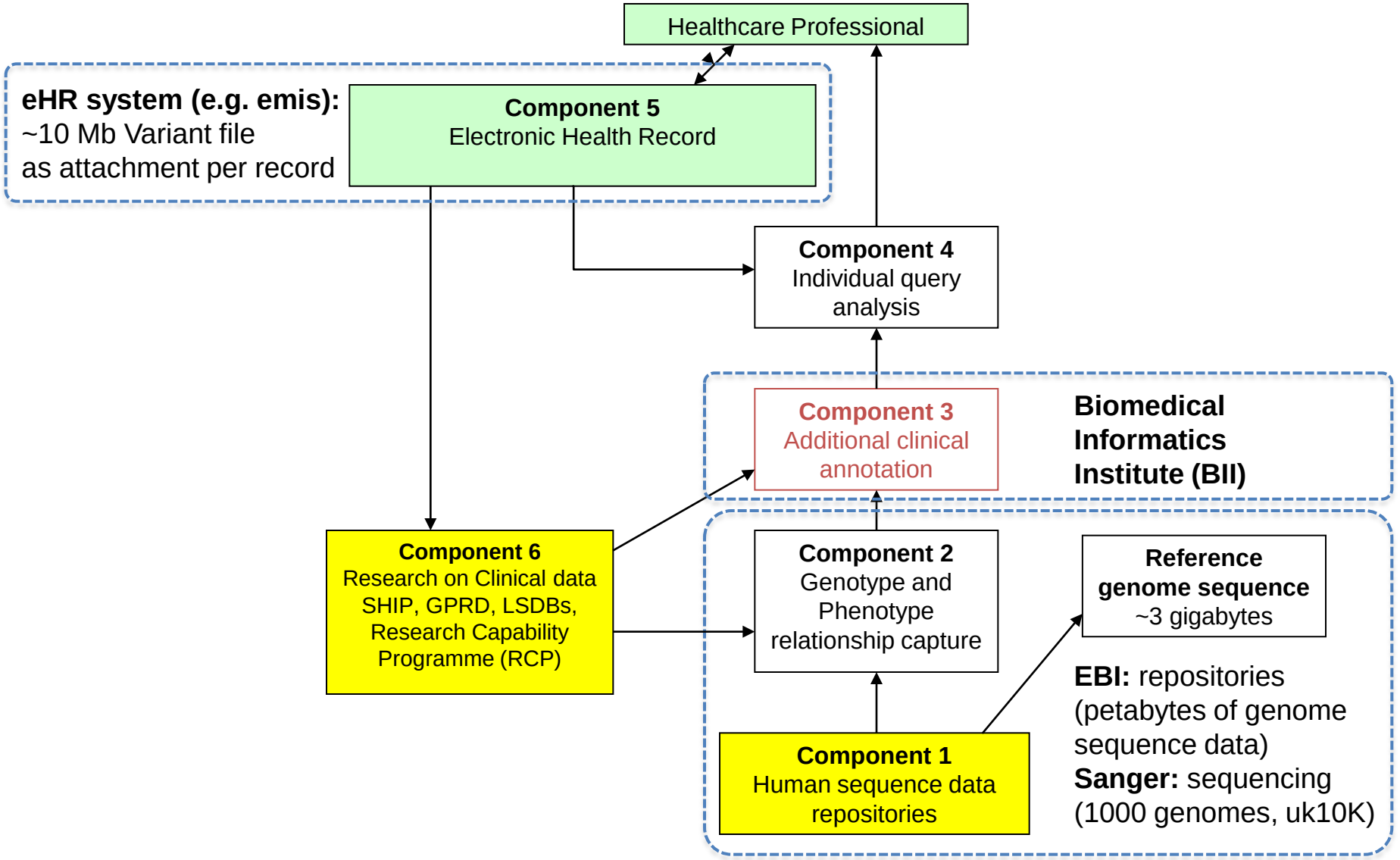
Components for Genomic Medicine



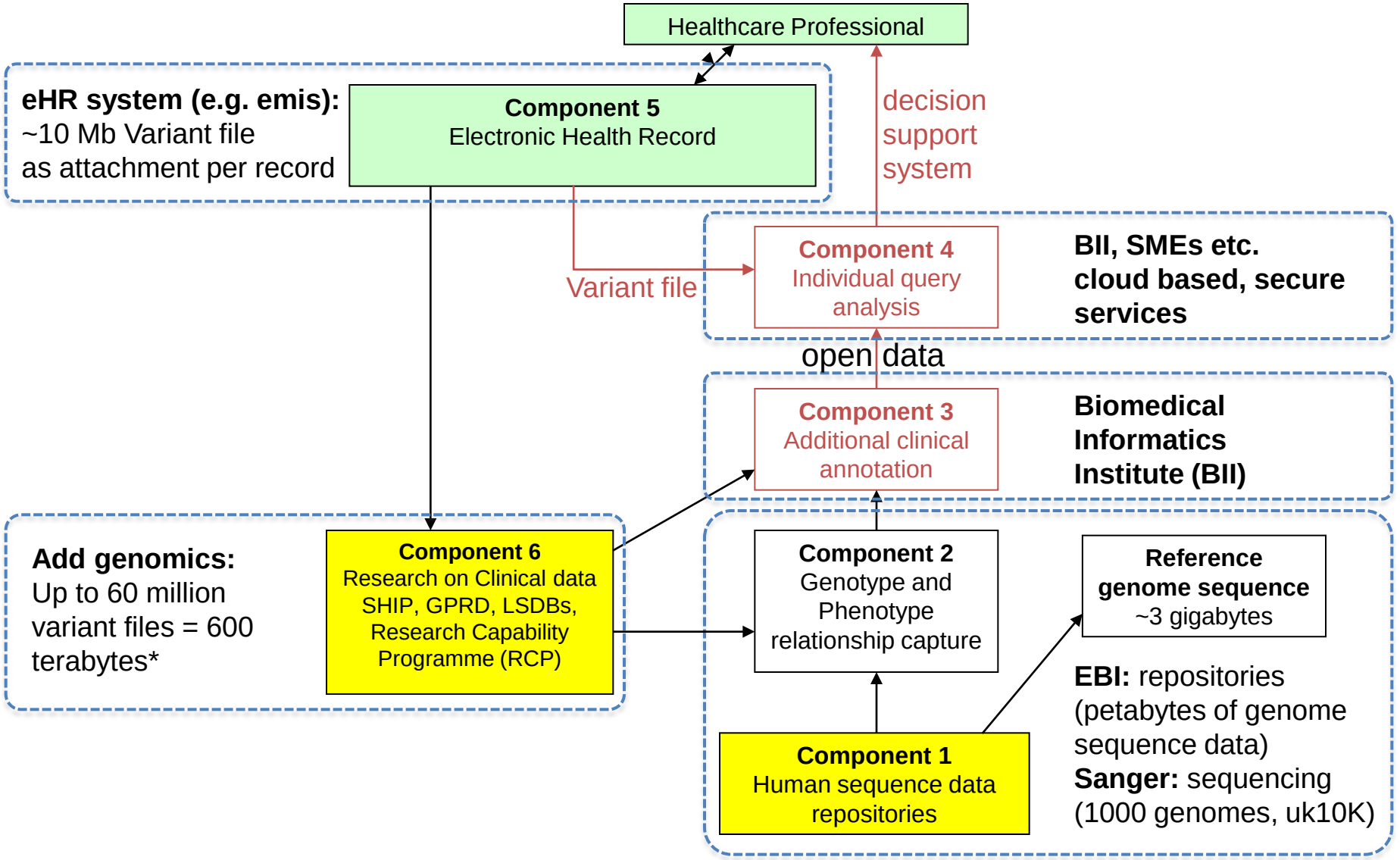
Components for Genomic Medicine



Components for Genomic Medicine



ICT Components for Genomic Medicine



Handling other genomic data

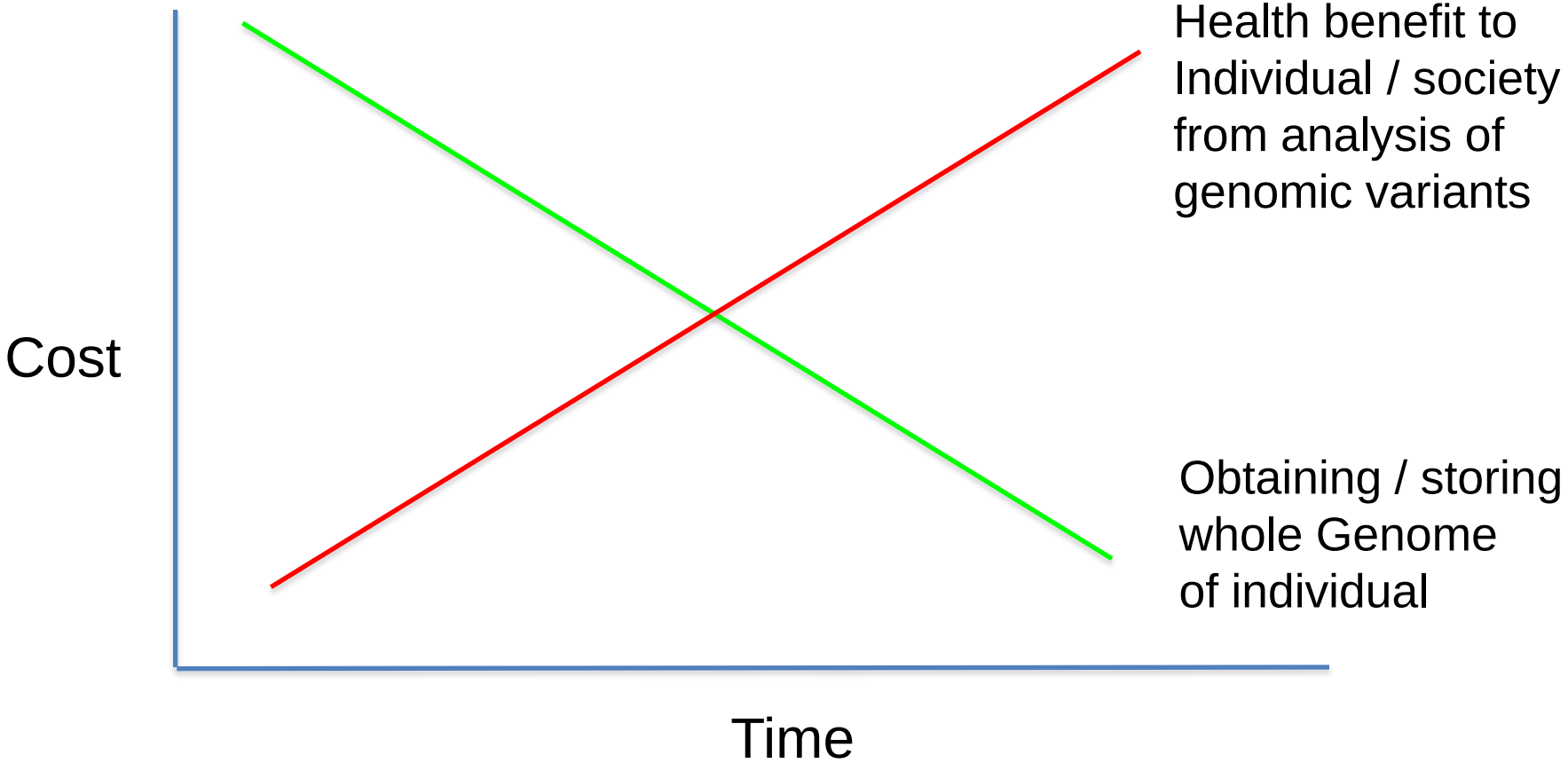
- Cancer
  - can still reduce genomes to summary files, but need to store more information: ~100Mb?
    - normal + potentially multiple cancer genome sequences (samples over time)
    - data about genome amplifications / deletions as well as genome sequence
- Pathogens / Microbiome
  - smaller genomes, more variable, many per individual, changing over time
    - reduction to summary data possible where reference genome known

Variant / Phenotype vs Health Economics

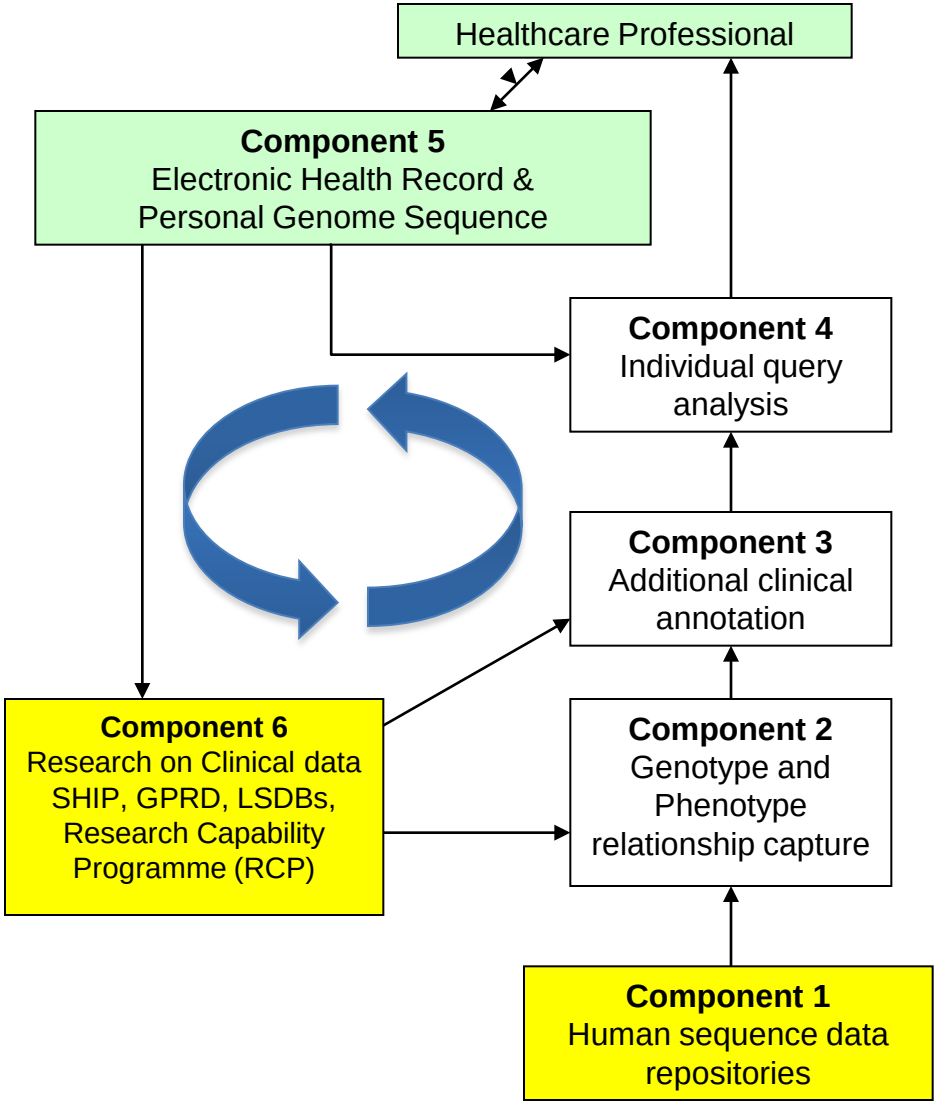
- Research databases:
  - Millions of single nucleotide polymorphisms (SNPs) and other variants catalogued
  - Thousands of variants linked to phenotypes at gene level
- Clinical databases:
  - Small number of variants known to have clinical effect; stored in geographically distributed locus specific databases (LSDB); not systematic
  - Very limited number of variants commissioned for clinical use (pharmacogenomics, stratified medicine)

What is the potential health economic value?

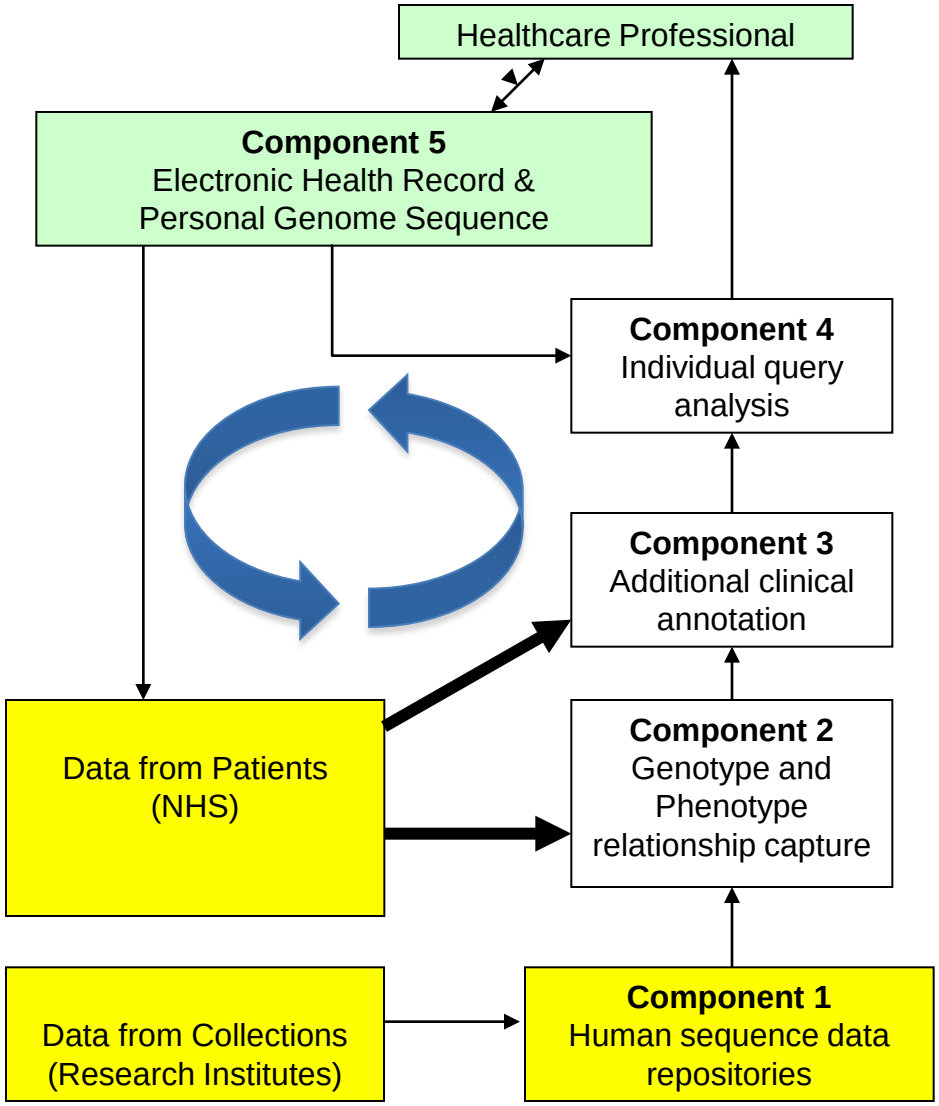
Cost benefit analysis



Components for Genomic Medicine



Components for Genomic Medicine



Beyond Genomic Medicine

EU FET Flagship pilot: IT Future of Medicine (ITFoM)

The project outcomes will enable the prediction of health, disease, therapy and its effects for individual patients and through application in the clinic will change the future of medicine.

For more information:
Website: **http://www.itfom.eu**
Email: **info@itfom.eu**
Twitter: **@itfom**
Facebook: **I.T. Future of Medicine**
LinkedIn**: IT Future of Medicine**

Acknowledgements

OSCHR E-health Board

Human Genome Strategy Group

Sanger Personal Genomes Working Group

PHG Foundation nextgen sequencing steering group

Many others for discussions

Summary - practicality

- feasible to capture unique features of an individual genome in small variant file and easily reuse
  - store as attachment to electronic health record (eHRs) within existing systems
  - real time comparison to reference set of annotated variants via lightweight secure web services
- aggregated data stored for research will eventually be large, but still manageable
  - information in variant files will need to be reorganised to allow complex analysis; results will feed into databases of annotated variants

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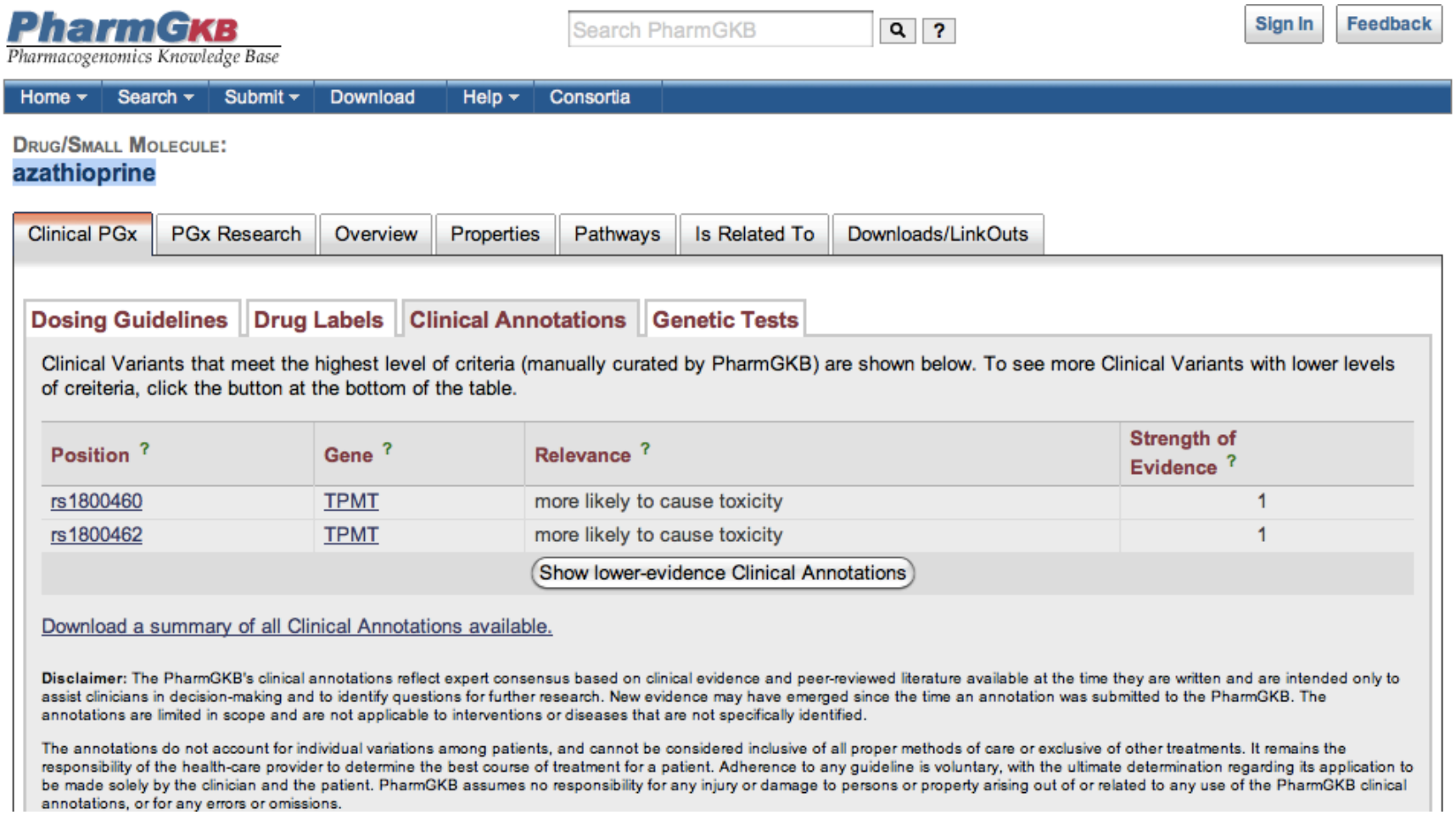

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DRUG/SMALL MOLECULE:
azathioprine

Clinical PGx | PGx Research | Overview | Properties | Pathways | Is Related To | Downloads/LinkOuts

Dosing Guidelines | Drug Labels | Clinical Annotations | Genetic Tests

CPIC Dosing Guideline - azathioprine, TPMT

Guidelines regarding the use of pharmacogenomic tests in dosing for azothioprine, thioguanine and mercaptopurine have been published in Clinical Pharmacology and Therapeutics by the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Download: article and supplement

Excerpt from the thiopurine dosing guidelines:

> Thiopurines are most commonly used to treat nonmalignant conditions but are also critical anticancer agents. The approach to dosing adjustments based on TPMT status may differ depending on the clinical indication and the propensity to initiate therapy at higher vs. lower starting doses. We and others advocate testing for TPMT status prior to initiating thiopurine therapy, so that starting dosages can be adjusted accordingly.

Recommended dosing of azothioprine by TPMT phenotype

Phenotype (Genotype)	Examples of diplotypes	Implications for azathioprine pharmacologic measures	Dosing recommendations for azothioprine	Classification of recommendations
Homozygous wild-type or normal, high activity (two functional *1 alleles)	*1/*1	Lower concentrations of TGN metabolites, higher methylTIMP, this is the "normal" pattern	Start with normal starting dose (e.g., 2-3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.	Strong
Heterozygote or intermediate activity (one functional allele - *1, plus one	*1/*2, *1/*3A, *1/*3B, *1/*3C,	Moderate to high concentrations of TGN metabolites; low concentrations of	If disease treatment normally starts at the "full dose", consider starting at 30-70% of target dose (e.g., 1-1.5 mg/kg/d), and titrate based on tolerance. Allow 2-4 weeks to reach steady state after each dose adjustment.	Strong

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Links to PharmGKB summary data for variants. PharmGKB variant annotations provide manually curated information about variant-drug pairs based on individual PubMed publications.

view legend

	Gene ?	Variant ? (build 132)	Alternate Names ?	Drugs ?	Alleles ?	Function ?	Amino Acid ? Translation
CA VA	DDRGK1 ITPA	rs1127354	ITPA, ITPA: 94C>A, P32T, c.43C>A, c.94C>A, g.3133842C>A, g.3133842C>G, g.3141842C>A, g.8787C>A, p.Pro15Thr, p.Pro32Thr	azathioprine	C > A	Missense	Pro32Thr
CA	NHLRC1 TPMT	rs1142345	TPMT*3C, c.719A>G, g.18238897T>C, g.29457A>G, p.Tyr240Cys	purine analogues mercaptopurine azathioprine	T > C	Missense	Tyr240Cys
CA	TPMT	rs1800460	TPMT*3B, c.460G>A, g.18247207C>T, g.21147G>A, p.Ala154Thr	purine analogues mercaptopurine azathioprine thioguanine	C > T	Missense	Ala154Thr
CA	TPMT	rs1800462	TPMT*2, TPMT:238G>C, c.238G>C, g.16420G>C, g.18083955C>G, g.18251934C>G, p.Ala80Pro	purine analogues mercaptopurine azathioprine thioguanine	C > G	Missense	Ala80Pro
VA	AOX1	rs55754655	AOX1: c.3404A>G, Asn1135Ser, c.3404A>G, g.51735748A>G, p.Asn1135Ser	azathioprine	A > G	Missense	Asn1135Ser

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- As of 12/10/11
  - 412 variants associated with drug
  - 66 drugs with variants associated with them

- What would be the health economic benefit of using these variants across a population?
  - Currently unknown

Summary – policy

- Clinical Services to analysis whole genomes require a database of variants
  - validated for clinical effect and health economics value
- Network of open, federated national databases is appropriate
  - nationally specific (linked to National drug lists; genetic population structure) but can build on internationally data
  - Free data access will incentivize service development (c.f. UK mapping data) and enable international data sharing
- The health value of variants in the database will increase
  - Requires research over Health records and associated genetic data

Application areas

1. Personal genome sequence
   - Explain rare genetic defects (now: low resolution arrays)
   - Personalise drug prescription, dose (now: rarely done)
   - Assessment of disease risk (now: single gene tests; entertainment)
2. Cancer genome sequence
   - Design treatment based on exact genetic defect (now: expression microarrays / correlations)
   - Watch for reoccurrence
3. Pathogen genome sequences
   - Identifying cause of illness (now: lengthy culture)
   - Tracking evolution and spread of epidemic (now: culture based)
   - Treatment that takes into account personal gut flora (now: unknown)

Starting point for Personal Genome Sequence:

- Will be as cheap to obtain and store full genome sequence as carry out any existing specific test
- Subsequent ‘tests’ will have negligible cost (IT costs alone) and be near instant
  - Changes health economics and practicality of ‘tests’ for clinical decision making

What is needed to enable this?