The 100,000 Genomes Project and Genomics England

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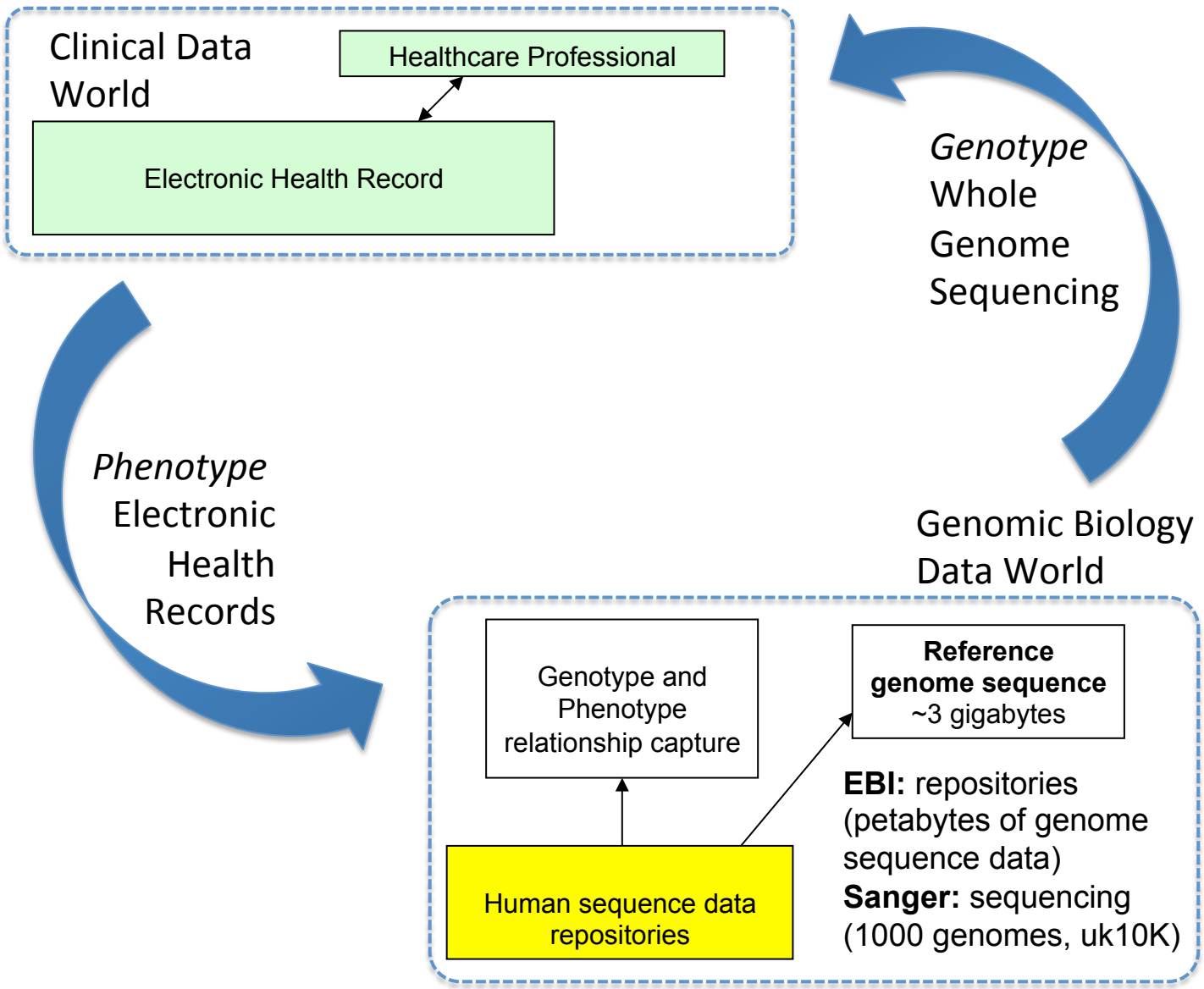
From Systems Medicine to Personalized Health
31st March 2014, Bern

Linking Health data to Research



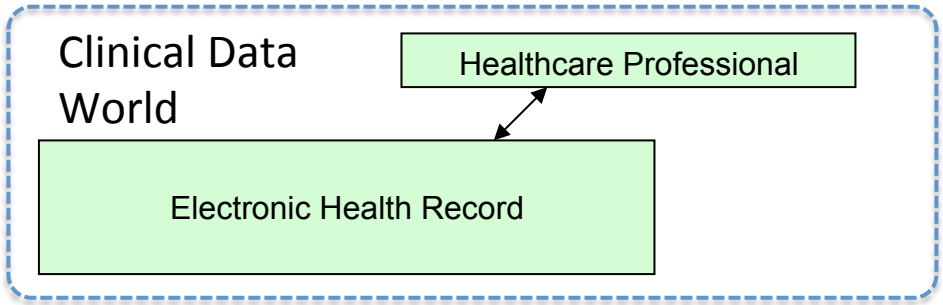
Steps in UK towards E-Health Research, Genomic Medicine

- Health data to Research
  - 2006 Creation of OSCHR
    - Increase coordination between funders: MRC and NIHR
  - 2007 OSCHR E-health board
    - Enable research access to UK EHR data
    - Build capacity for research on EHR data
- Genomics to Health
  - 2009 House of Lords report on Genomic Medicine
  - 2010 Creation of Human Genomic Strategy Group (HGSG)

2011: UK Life Sciences Strategy

No10: http://www.number10.gov.uk/news/uk-life-sciences-get-government-cash-boost/
BIS/DH: http://www.dh.gov.uk/health/2011/12/nhs-adopting-innovation/

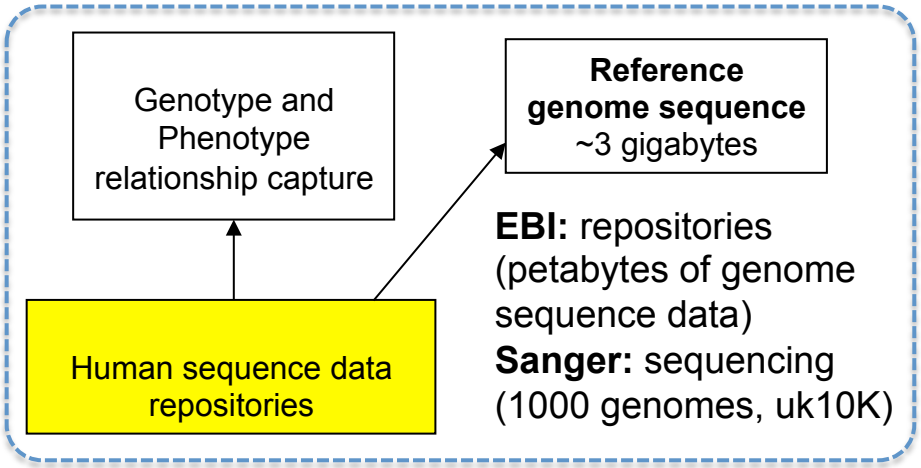
Linking Health data to Research



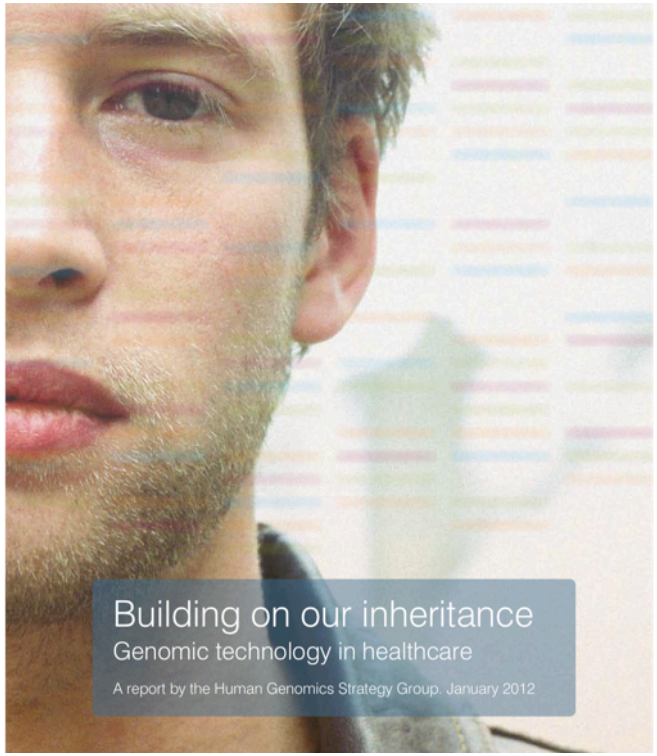
Clinical Practice Research Datalink (CRPD)

Phenotype Electronic Health Records

Farr Institute



2012: Human Genome Strategy Group report
UK Life Science Strategy Update; 100K Genomes



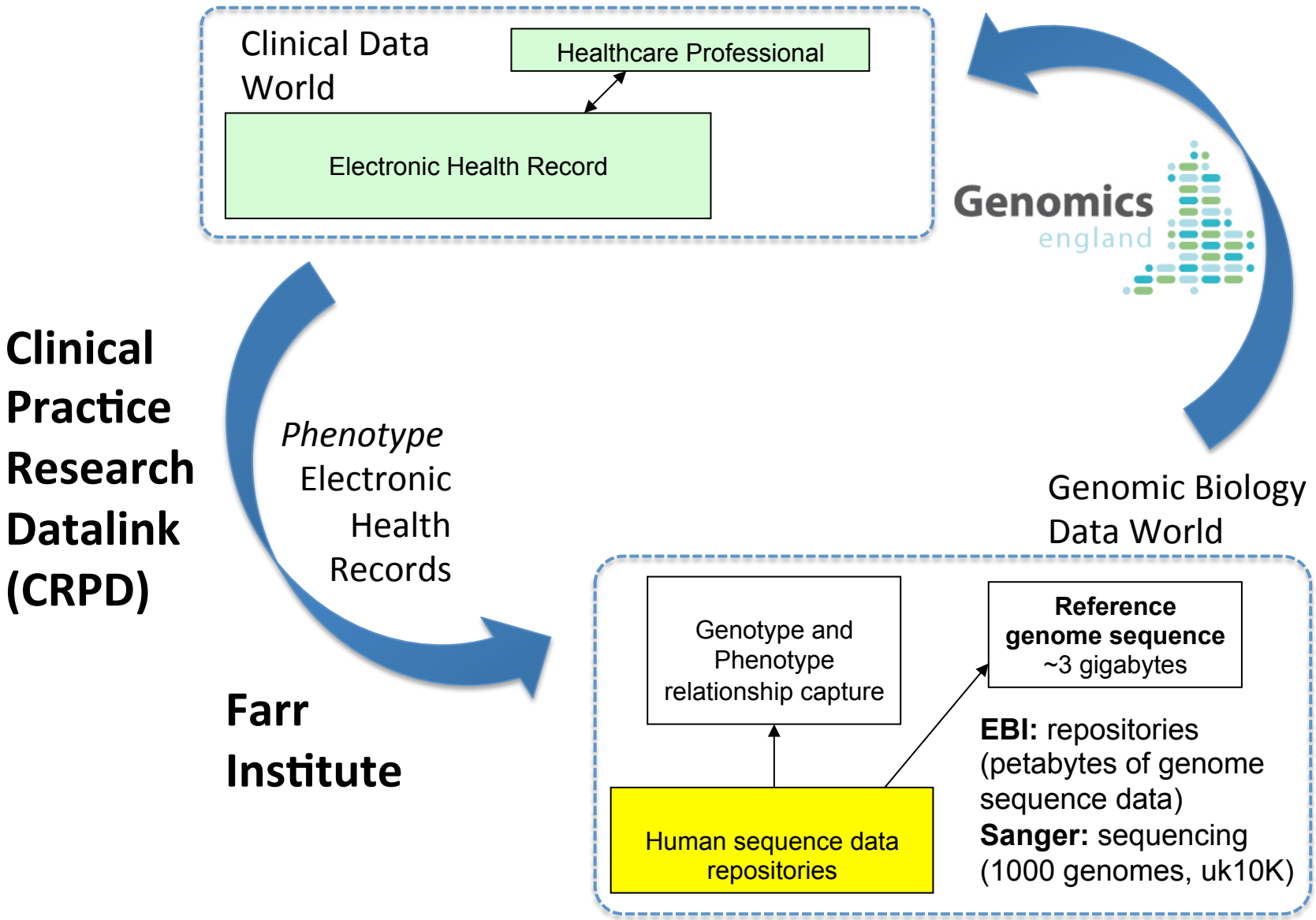
DH: http://www.dh.gov.uk/health/2012/01/genomics/
BIS: http://www.gov.uk/office-for-life-sciences/

Genomics England

http://www.genomicsengland.co.uk/

@genomicsengland

Linking Health data to Research



Genomics England- mission

- 100,000 patients with rare inherited disease, common cancers and pathogens from the NHS in England
- Whole Genome Sequencing
- Generate improved health and wealth for UK
- Legacy of infrastructure, human capacity and capability
- Become World-leader in Healthcare application of Genomic Medicine
- £100m funding over the next 5 years

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Scale compared to existing WGS

- 1000 genomes and UK10K
  - low coverage genomes (~4x illumina)
- Limited number of 'clinical grade' WGS
  - TCGA: ~700
  - ICGC: ~700
  - WGS 500: 500

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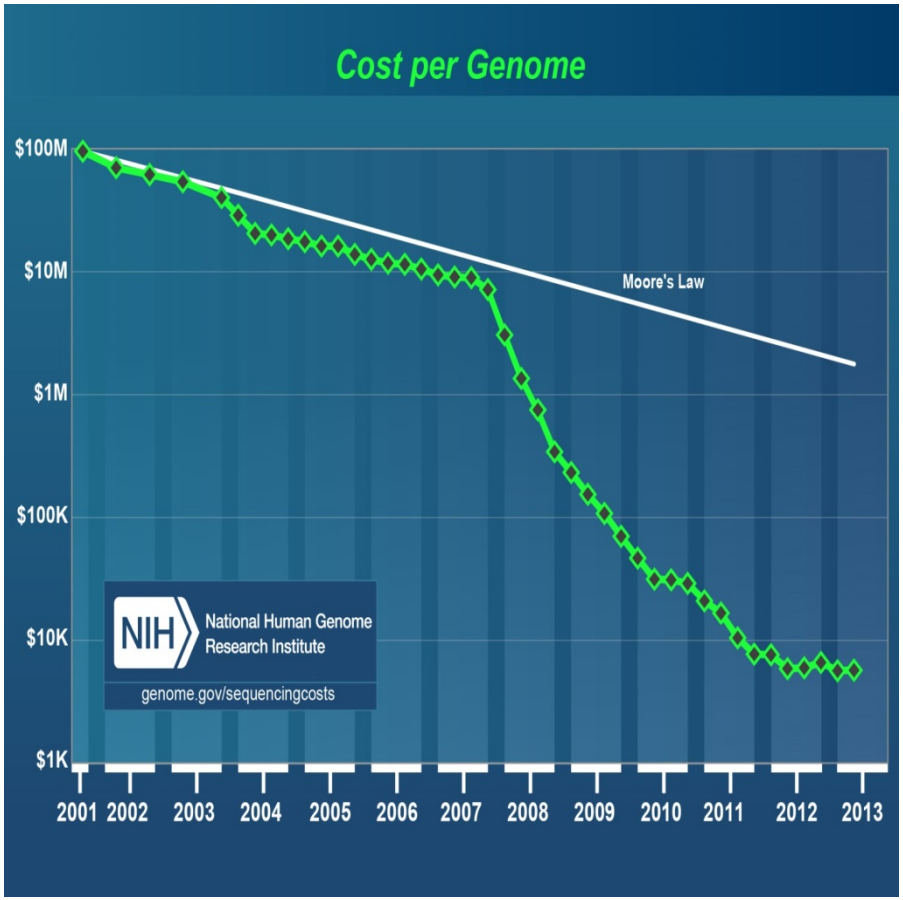
Is now the moment to commit to WGS



Data Type	Large-scale structural changes	Balanced translocations	Distant consanguinity	Uniparental disomy	Novel/known coding variants	Novel/known non-coding variants
Targeted gene sequencing	⊗	⊗	⊗	⊗	☑	⊗
SNP arraya	☑	⊗	⊗	☑	☑	⊗
Array CGH	☑	⊗	⊗	⊗	⊗	⊗
Exome	☑	⊗	⊗☑	⊗☑	☑	⊗
Whole Genome	☑	☑	☑	☑	☑	☑

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WGS500 Results

- 7 Novel genes for disease
- 6 Novel phenotypes for known genes
- 2 pathogenic regulatory variants in or downstream of known candidate genes
- 6 genes missed by prior Sanger Sequencing

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Of 95 families, to date

- 23 families have new clinical diagnosis
  - NB pre-screened for known genes
  - result will increase with follow-up
- 74 families in follow up studies
- Over 50% of these have strong lead candidate

Rare inherited diseases

- >5% of the population
- 7000 rare disorders- disabling, shorten life, costly
- Circa 85% have a single gene defect
- Early knowledge may avoid disability
- Testing for >700 disorders extant within the NHS diagnostic laboratory network (UKGTN)
- Represents <1/4 of known disease genes.
- Whole Genome Sequencing 25-50% increase in discovery

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Genomics England – Rare Disease Partnering opportunities

- NIHR Translational Research Collaborative
- NIHR BioResource
- £20m for deeper phenotyping
- Decipher & Deciphering Developmental Disorders
- NHS Clinical Genetics Service
- Farr Institute
- International Rare Diseases Research Consortium
- US and EU programmes

Cancer

- Lung Cancer -40 000 cases/year in the UK, (35K die/year)
- Largest cause of cancer death, therapies modestly effective only applicable to 10-15% of patients
- CRUK Stratified Medicine's initiative

- Other Cancers - Breast, colon, prostate and unknown primary

- Rare and Childhood Cancers

- Drugs target mutations
- Tumour heterogeneity

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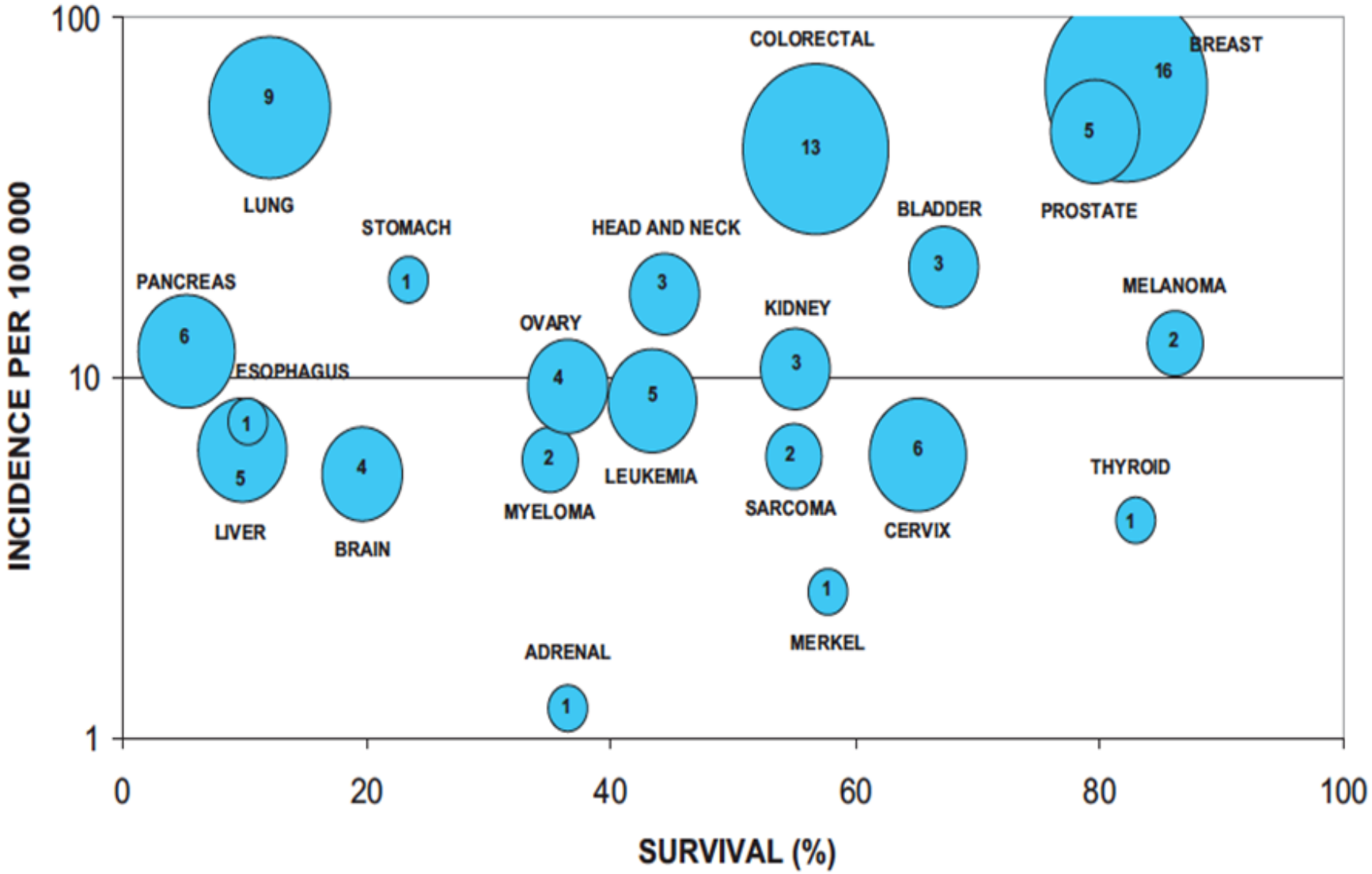
Incidence v survival at 5 years



Pathogens

- Stratifying response, minimising adverse events and tracking outbreaks
- M. Tuberculosis resistance and epidemiology
- Hepatitis C genotype selects therapy
- HIV –Treatment for life and resistance testing is in the care pathway.
- Extreme human response to sepsis
- International linked datasetss

Public Health England

Genomics England Pilots

- Phase 1- Sequencing and Annotation Competition – now
- 4 providers 15 samples (5 tumour – normal pairs and 5 germline)
- Testing Sequencing QA and annotation

- Phase 2a-2000 Rare Inherited Disease WGS- 30x depth – over 2014
- Partnering NIHR BioResource and Translational Research Collaborative
- 5 centres - 928 samples since end of November- 1st 96 are in sequencing.

- Phase 2b- 3000 Cancer Patients (Lung, Breast, Ovary, Prostate & Colon)
- Somatic (?50-80x) and germline (30-40x) – tendering now
- Optimise Molecular Pathology pipeline
- 11 CRUK Centres and BRCs

- Pathogens will be with Public Health England

Phase 3- Main Programme

- Preparation for main programme underway
- Formal procurement to take place mid 2014
- Biorepository to be established
- Data architecture – advanced planning
- Envisage 2 or more Sequencing Centres in England
- WGS expected volume:
- 20k in 2015; 30k in 2016; 40k in 2017
- Elasticity in the pipeline

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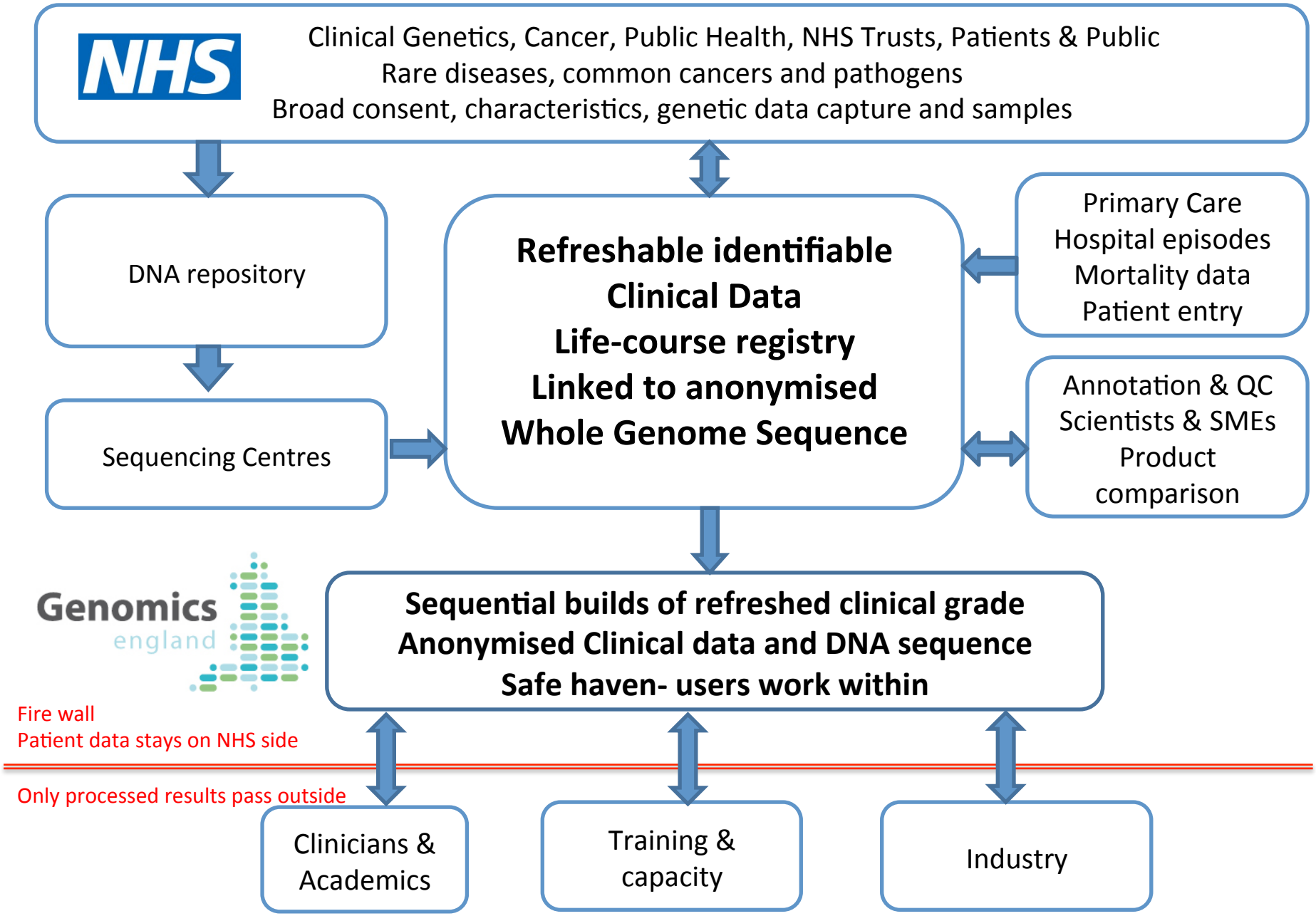
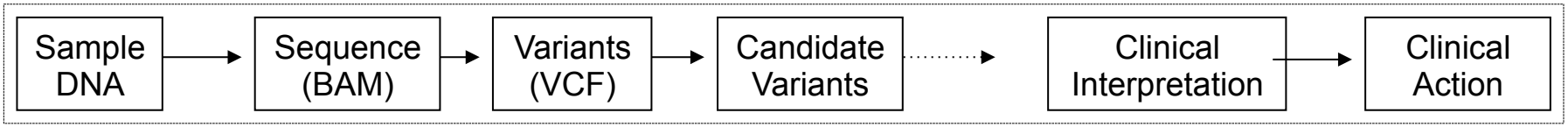
Genomics England – Operational Plan



Process Overview



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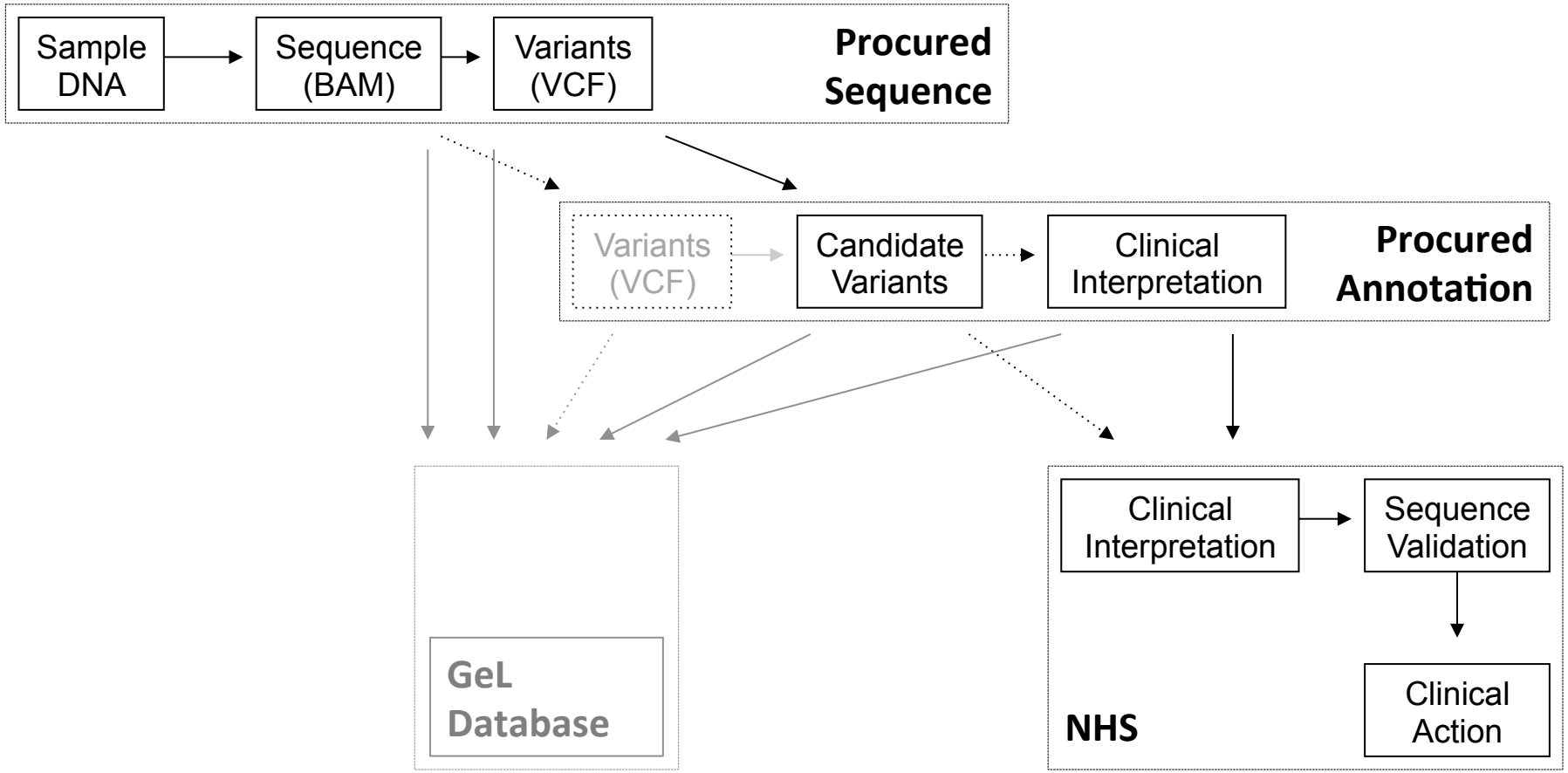
Process Overview



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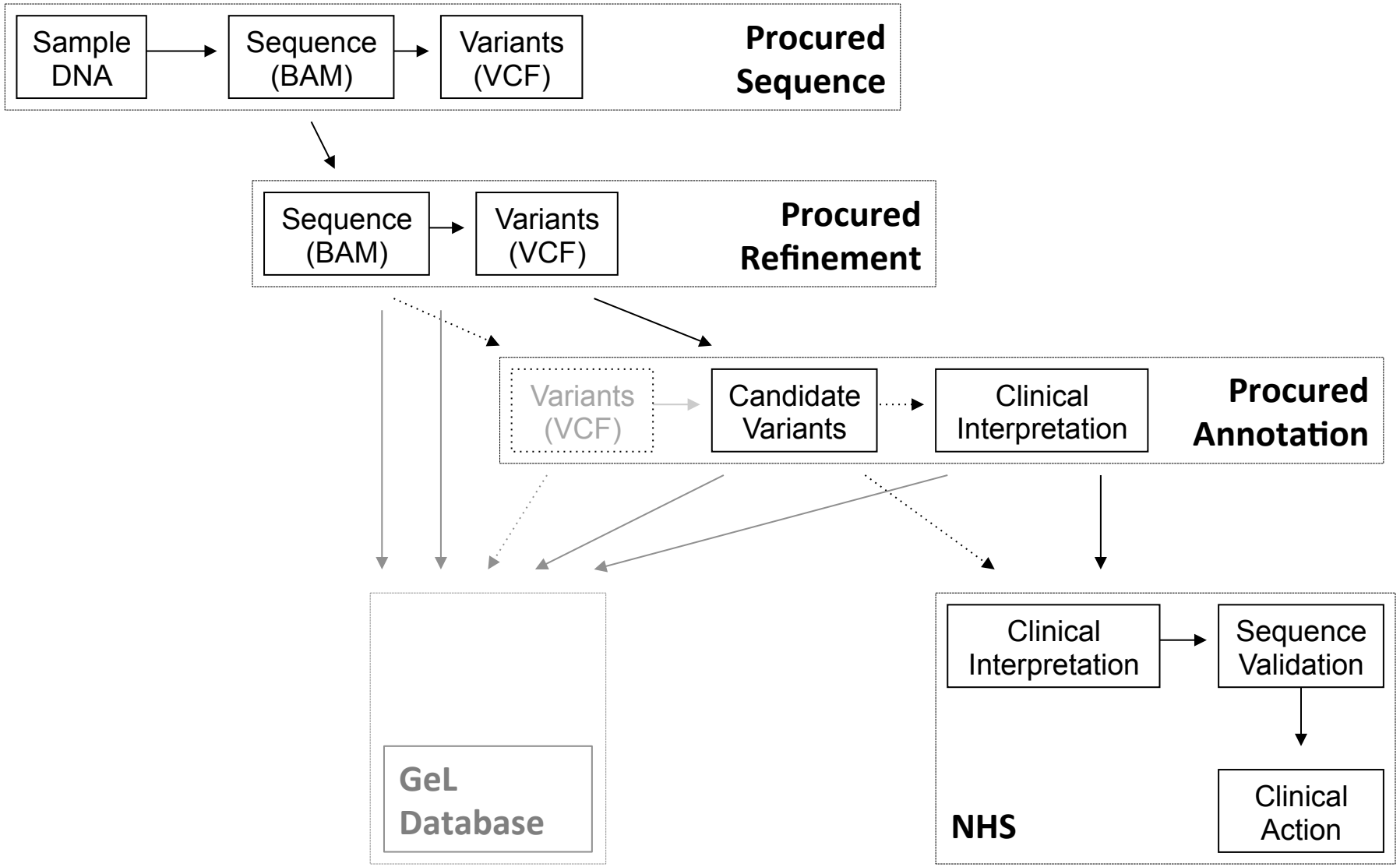

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Sequencing assessment

- Data returned by suppliers, being assessed
- Evaluation on quality and coverage

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Annotation assessment

- Harder than assessing sequencing
- Gold standard less well defined
- Lack of established data standards

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Past assessment exercises

- CASP – Critical Assessment of Structure Prediction (since 1994, CASP11 in 2014)
- GASP, RGASP – Gene prediction and RNAseq assessments

- CLARITY Challenge – 2012
  - http://genes.childrenshospital.org/
- CAGI – 2010, 2011, 2013
  - https://genomeinterpretation.org/

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Data provided by GeL

- Sequence from providers (BAM+VCF)
  - Rare diseases: trio
  - Cancer: germline + tumour
- Phenotype data available to clinicians

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Types of annotation anticipated

- Filtered, ranked lists of variants with estimates of pathogenicity and confidence
- Expected impact at level of genes, pathway
- Tools organising literature around affected genes, pathways
- Clear, simple clinical reports
- Suggested clinical interventions

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Assessment criteria

- Accuracy
- Clinically informative
- Rapid turnaround
- Understandable output
- Standardised output data formats
- Ability to operate at scale
  - 2014: ~25 samples/day (pilot)
  - 2015: ~50 samples/day
  - 2017: ~100 samples/day

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Bake offs (phase 1)
Initial annotation assessment

- Information collection exercise on 5+5 studies
  - Investigate levels of annotation available
- Minimal file format requirements
  - Will inform future specifications for file formats

- Will select multiple suppliers for pilot (phase 2)
  - Ability to deliver timely, consistent data, etc.

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Pilot (phase 2)
Ongoing annotation assessment

- Precise file format requirements, with optional sections

- Best suppliers will be invited to tender to provide annotation for main programme (2015-2017)

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Main programme (phase 3)
Annotation generates clinical feedback

- Software will run as Virtual Machines within GeL datacentre, c.f. Apps
- Software will be subject to evolving compliance requirements, c.f. CLIA dry lab

- No need for 'Apps' to be comprehensive: potential for specialist software, e.g. specific diseases, pharmacogenomics etc.

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UK Genomic Medicine Research Data Infrastructure

the Farr, Oxford, Cambridge, EBI, Sanger, UK Biobank, Newcastle, Dundee, Kings, QMUL (lead)

- MRC Clinical Research Capabilities Call
- International and National Research Platform
- Rich clinical dataset, enriched by e-health (Farr, UK Biobank), high fidelity sequence, QA and annotation
- Inter-operable flexible data centre 60PB and 10,000 cores connected to sequencing centres, partners and users
- Applications e.g. Decipher, Ensemble, ENCODE, user developed software
- Embassies for research and combining datasets
- Cost of Research Data Centre is £24m - timing is key

Engaging with this programme

Clinical Interpretation Partnership
Academics, NHS, Philanthropy and Funders

Research Engagement

- 2000 –extending Rare disease to 6000
- Cancer just starting now 3000 aimed for.
- PHE – Pathogen Pilots

- Designate Genomics England Centres
- Local Lead and extended team
- High fidelity phenotypes and quality DNA
- Genomics England owns the data
- Clinical Interpretation Partnership
- Access to data on the samples
- 6 months protected space to analyse and submit
- Co-authors on papers

Multi-omics Cancer Repository

- RNA transcriptomics, micro RNAs
- Epigenetics, Proteomics and metabolomics
- Cell free circulating DNA (liquid biopsy)
- Sequential biopsies & WGS (trials)
- Immortal Cancer Cell Lines for drug sensitivity, single cell physiomics or functional genomics

- Harness the potential of MRC/NIHR Phenome Centres
- Experimental Cancer Medicine Centres
- International Cancer Genome Consortium and the Cancer Genome Atlas

- Barretina, J. *et al. Nature* **483**, 603-607, (2012).
- Garnett, M. J. *et al. Nature* **483**, 570-575, (2012).

Stratified medicine and therapeutic innovation

- Rare Inherited Disease – sub-phenotypes
- Priming functional studies at single cell, tissue, experimental models and the human Lab
- Therapeutic innovation or repurposing

- Cancer – Molecular pathology
- Priming functional studies at single cell, tissue, experimental models and the human Lab (strategic aim 1)
- Therapeutic innovation, repurposing or stratified medicine

- Pathogen resistance, epidemiology of disease outbreak
- Stratified healthcare link to PHE Reference labs and human data
- Opportunity for pathogen research

International Partnership

- Ethical and communications research - creating and partnering to set global standards

- Competitor or partner programmes
- Veterans Administration
  - Large cohort (1M), contract let for 5000 WGS
- US Integrated Healthcare Systems
  - Scripps – Wellderly Study sequenced 2000 volunteers to study lifestyle
  - Inova Health – aims to provide worlds larges WGS database, 1500 completed thus far
- Clinical Research programmes
  - Oxford 500 WGS, DDD (Sanger) up to 12,000 children (mainly exomes)
  - International Rare Diseases Consortium/Orphanet
  - International Cancer Genome Consortium
  - St Jude and Moffit Cancer Centres
  - Middle Eastern programmes
  - Chan Shoon-Shiong Foundation
  - Pharma and SMEs
  - Personal Genome Project – aims for 100k, all open data

Universities and NHS Education

- Health Education England
- UK Medical Schools

- Genomic medicines transformative potential needs an enabled healthcare team
- Needs a national approach
- Next generation sequencing
- Diagnostic potential in rare disease
- Stratified medicine in cancer
- Pathogen drug resistance
- Bioinformatics

Genomics England

- 100,000 WGS on NHS patients and pathogens
- Aware of the challenges
- Working with NHS, academics and industry to drive Genomic Medicine into the NHS
- Support that with education
- Leave a legacy of NGS Centres, sample pipeline and biorepository, large-scale data store that makes this usable by the NHS
- New diagnostics and therapies and opportunities for patients
- By end of 2017

NHS England

Public Health England

NHS National Institute for Health Research

CANCER RESEARCH UK

Acknowledgements

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