“The Grand Challenge”
optimising CDx R&D for use in clinical trials
in support of Precision Medicine

Will Spooner

Commercial Programme delivery lead, Genomics England
will.spooner@genomicsengland.co.uk

Pistoia Alliance Symposium:
Aligning Research with Clinical Standards in Support of Precision Medicine

Monday, 1st July 2019
Royal Society of Chemistry, Piccadilly, London
Aligning research with clinical standards
So what?

• Faster translation of research biomarkers into molecular diagnostics
• Faster clinical adoption of improved assay technologies and protocols

Better companion diagnostics sooner and cheaper

• More effective precision medicine development
• Reduced cost of precision medicine development

Better precision therapeutics faster and cheaper

PATIENT BENEFIT
About Genomics England

- Limited company, 100% owned by the UK Government Department of Health and Social Security.
- Acknowledged world leader in genomic medicine having successfully delivered the 100,000 Genomes Project.
- NHS delivery partner for the Genomic Medicine Service; the world’s first clinical whole genome sequencing service.
- A mandate to stimulate academic and industry research in precision medicine.
Where we are today

**Samples**
- **120,500**
  - Samples collected from NHS GMCs and sent to biorepository
- **36,859** cancer
- **83,641** rare disease

**Genomes**
- **109,072** Genomes sequenced
- **24,782** cancer
- **84,290** rare disease

**Analysis and Results**
- **76,527** genomes sent to NHS GMCs

**Research**
- **91,271** Data release of genomes in RE
- **2,424** GeCIP members with access to RE
- Over **100** Discovery Forum members (13 full members)

Figures as at 26/04/2019

02 July 2019
Genomics England’s world-leading dataset
February 2019 data release (v6)

One billion unique genotypes
100 trillion individual genotypes

Genomes
- 91,271 genomes
  - 22,091 Cancer
  - 69,172 Rare Disease

Primary clinical data
- 94,285 participants
  - 20,475 Cancer
  - 73,810 Rare Disease

Secondary data
- Hospital Episode Statistics (HES)
- Diagnostic Imaging Dataset (DID)
- Patient Reported Outcome Measures (PROMs)
- Mental Health Services Data Set (MHSDS)
- Office for National Statistics (ONS)
- Systemic Anti-Cancer Therapy Data Set (SACT)

Clinically interpreted data & QC
- 21,873 families with Tier 1, 2 and 3 variants from interpretation pipeline
- 4,763 families with GMC exit questionnaires
- 45,743 tiered and quality checked rare disease genomes; 19,098 quality checked cancer genomes

Quick view tables
- Key information from different tables, merged and filterable
- Merged with QC data
- Allow cohort-building and project feasibility assessment

10 million health records, over 100 per patient
Example: TMB testing in lung cancer

- BMS CheckMate 227 study: Progression-free survival significantly longer with first-line nivolumab plus ipilimumab than with chemo for patients with NSCLC and a high tumor mutational burden (TMB). TMB was determined by a Foundation One CDx assay.

- Our data shows discrepancy in TMB between Foundation One genes (FFPE samples) and WGS (FF samples). Possible basis for an improved TMB test based on FF-WGS?

TMB for 61 paired FF/FFPE: All genes WGS (FF samples) vs Foundation One genes (FFPE samples)

Comparison of FF-WGS TMB test with simulated Foundation One TMB test
Wide variation in TMB across many tumour types

Mutation burden across different tumour types

- Prostate
- Sarcoma
- Hepatic-pancreatic
- Breast
- Adult Glioma
- Ovarian
- Renal
- Endometrial Carcinoma
- Upper Gastrointestinal
- Colorectal
- Bladder
- Lung
- Malignant Melanoma

Total number of somatic non-synonymous small variants per Mb of coding sequence

02 July 2019
John Ambrose & Alona Sosinsky, Bioinformatics at Genomics England

Confidential
Going up a gear: the UK genomics vision
2nd October 2018

Matt Hancock the Secretary of State for Health and Social Care, announced an ambitious five year vision for genomic healthcare in the UK...

"Expansion of the 100,000 Genomes Project to one million whole genomes sequenced by NHSE and UK Biobank in the next five years"

"From 2019, the NHS will offer whole genome analysis for all seriously ill children with a suspected genetic disorder, including those with cancer. The NHS will also offer the same for all adults suffering from certain rare diseases or hard to treat cancers"

"An aspiration to sequence 5 million genomes in the UK within the next five-year years"
100,000 Genomes a year

• UK is world’s first health system to commission whole genome sequencing as standard of care
  • Rare disease
  • Cancer

• Need accreditation to avoid need for confirmatory testing
  • ISO 15198 obtained
Pool of participants for clinical trials

- Research-consented participants (as of Feb 2019):
  - 20,000 participants with cancer
  - 35,000 participants with rare disease
  - 40,000 unaffected relatives

- Pre-screen for referral to clinical trials

More than this *per year* through the NHS Genomic Medicine Service
BPM 31510 is BERG's lead molecule currently in phase I and II trials. Its development and clinical trials have been guided by the BERG Interrogative Biology® platform.

BPM 31510 was granted FDA Orphan-Drug Designation for the treatment of Pancreatic cancer in Jan 2018.

Genomics England provides genome sequencing and longitudinal follow up for UK study participants.
• BIIB078 is a Biogen antisense oligonucleotide drug designed to inhibit translation of mutated copies of C9ORF72 that cause a rare form of familial ALS

• Recruitment to rare disease trials like this is slow and suffers from high screen failure rate

• We aim to use the Genomics England dataset to accelerate recruitment to this trial through referral of pre-screened participants
Fly in the ointment

• **But** confirmatory testing will still be needed. Health Institute Exemption not good enough.
• The opportunity?
  • Prescription of medicines according to a patient’s full genome,
  • Targeting of treatments to those most likely to benefit without the need for re-testing.
  • Establishing the regulatory and reimbursement pathway,
  • Establishing testing lab capability and standards.
• Why the UK?
  • Range of unique assets; NHS, pathways for FF-WGS, academic strength
  • Planned introduction of WGS into clinical care
  • Commitment from government, Life Science Sector Deal;
    • UK Biobank and ADD
    • Digital Innovation Hubs
    • Genomic Medicine Service
WGS-IVD workshop, March 2019

• Who benefits?
  • Patients and the NHS
  • UK life science sector
  • UK science and academia
• When?
  • Many national programmes.
  • Significant industry investment.
  • Window of advantage in the UK: 12-24 months.
Complex regulatory space

• How will labs and genome testing processes be accredited for WGS?
• What standards, accuracy/reliability of genomic testing will regulators require?
• How will relevant software and algorithms be approved for transmission, storage, retrieval and analysis of genomic data?
• What analytic and clinical requirements will need to be met (both to ensure accuracy of test results and that the desired clinical effect is achieved)?
• How will ‘informed consent’ work for re-use of WGS data for future targeted treatments?
Work has started on designing a Regulatory Pathfinder

- Analytical performance
  - Equivalence of WGS with an existing approved test
  - Standards; e.g. NIBSC BCR-ABL

- What to test
  - Tumour biomarkers (tumour genome)?
  - Pharmacogenomic biomarkers (germline genome)?

- How to test
  - Integration into the Genomic Medicine Service, testing existing pathways
Summary

• By aligning regulators, industry and the NHS, the UK is ideally placed to catalyse the launch of the first innovative medicine based on WGS.

• The UK has an opportunity to lead the way in establishing a regulatory and reimbursement pathway, and testing lab capability and standards.

• A “Regulatory Pathfinder” initiative is a pragmatic next step in navigating the complex regulatory landscape.
<table>
<thead>
<tr>
<th>Email</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="mailto:commercialpartnerships@genomicsengland.co.uk">commercialpartnerships@genomicsengland.co.uk</a></td>
<td></td>
</tr>
<tr>
<td><a href="mailto:will.spooner@genomicsengland.co.uk">will.spooner@genomicsengland.co.uk</a></td>
<td></td>
</tr>
<tr>
<td>@genomicsengland</td>
<td>#genomes100k</td>
</tr>
<tr>
<td>Like the ‘Genomics England’ page</td>
<td></td>
</tr>
<tr>
<td>Follow ‘Genomics England’</td>
<td></td>
</tr>
<tr>
<td>Newsletter: <a href="http://www.genomicsengland.co.uk/sign-up">www.genomicsengland.co.uk/sign-up</a></td>
<td></td>
</tr>
<tr>
<td><a href="http://www.genomicsengland.co.uk">www.genomicsengland.co.uk</a></td>
<td></td>
</tr>
</tbody>
</table>
By taking into account individual variability in genes and environment for each person it will be possible to develop better treatment faster and cheaper.

Application of knowledge from linked genotypic-to-health information Across the R&D pipeline

- Identification of targets and mechanisms linked to disease and drug response
- Improved therapeutic index in selected patient populations
- Superior safety & efficacy in pre-determined patients
- Optimisation of patient care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target discovery</th>
<th>Pharmacology Safety</th>
<th>Clinical Development</th>
<th>Regulatory approval</th>
<th>Post-marketing</th>
</tr>
</thead>
</table>

| Diagnostic | Biomarker discovery | Analytical validation | Clinical validation | Regulatory approval | Clinical practice |

Over 100 drugs in clinical trials with CDx indicated
Sixty-three approved CDx tests, multiple indications