The impact of germline genetics on breast cancer and integration in clinical practice

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Cancer genomics is important in two contexts.
Breast cancer predisposition

Common
low penetrance
90 variants

Rare high/mod penetrance

Allele Frequency

Relative Risk

BRCA1
BRCA2
PALB2
CHEK2
PTEN
CDH1
STK11
TP53
BRCA1
Cancer predisposition genes have high clinical utility

- Improved diagnosis
- Optimised management and follow-up
- Tailored therapies
- Information for relatives
- Cancer prevention
- Cost efficiency

Strong clinical and economic rationale for greater genetic testing of cancer predisposition genes
We need to test more genes in more people
Limitations of current clinical cancer genetics

1. Clinically and molecularly a low-throughput system.
2. Developed to limit access to testing.
3. Highly complex referral and testing eligibility criteria.
4. Primarily arose to meet needs of unaffecteds.
5. Not serving the needs of cancer patients well.
Medical genetics
in people with cancer

vs

Predictive genetics
in healthy individuals
breast cancer 38 yrs

ovarian cancer 64 yrs  breast cancer 54 yrs

breast cancer 37 yrs

BRCA2
breast cancer 38 yrs

ovarian cancer 64 yrs  breast cancer 54 yrs

breast cancer 37 yrs
breast cancer 38 yrs
breast cancer 38 yrs

Oophorectomy

breast cancer 54 yrs

Mastectomy
Genetic testing in cancer patients is an effective and efficient way of preventing cancer
We need to offer testing to more breast cancer patients
??Genetic testing is easy??

Whole genome - $1000
Genetic testing is easy

Sequencing
Genetic Test

1. Sequencing
2. Analysis
3. Interpretation

REBYHINEIHESTTOTE
THE BOY IS IN THE TREE
HE MIGHT BE STUCK - GET A LADDER
Genetic Test

Patient Sample → Sequencing → Analysis → Interpretation → Clinical Report
Genetic Test

Patient Sample → Sequencing → Analysis → Interpretation → Clinical Report
TruSight Cancer™

**TruSight Cancer Panel (TSCP)**

- 97 Genes/gene regions
- 260 Cancer GWAS SNPs
- 24 Fingerprinting SNPs

- 1449 exons
- 1736 targets

- 287 SNPs
- 456 KB

0.01% of the genome

**Simple + Robust**
- Low input (50ng)
- Low failure rate
- Easy lab process

**High Capacity**
- 576 samples / week / HiSeq2500
- median 500X coverage

Majority of UK labs adopting TSCP

Shazia Mahamdallie
Anthony Renwick
Genetic test

Patient Sample → Sequencing → Analysis → Interpretation → Clinical Report
Analysis

Requirements for clinical genetic test analysis

- Fast
- Reliable
- Short hands on time

**TSCP – custom analysis pipeline**
< 1 min hands-on-time
No bioinformatician necessary
6-8 hours (overnight) for 96 samples

Tools available on http://www.well.ox.ac.uk/ogc/sequencing-tools
GAMA.sh
Begun by TGLclinical
Creates analysis folder and scripts from templates with create_jobs.R
Sends email notification

FASTQ_creation.sh
Runs CASAVA based on TGL's SampleSheet.csv
Sorts samples by fastq size into
Sends email when finished

BAM_creation_$i.sh
Alignment by Stampy
BRCA coverage evaluation

SmallVariant_creation_$i.sh
Variant calling by Platypus, CAVA annotation
BRCA test outputs by Sanger_creation_$i.R
Sends email if all variant calling is finished

LargeVariant_creation_$i.sh
Run modified ExomeDepth for each pool
Sends email if all variant calling is finished

Dedicated HPC cluster
8 nodes
12 cores per node

96 samples – 8 hours
Small + large mutations
>99% sensitivity and specificity

Tools available on http://www.well.ox.ac.uk/ogc/sequencing-tools

Elise Ruark, Marton Munz
Anna Fowler, Gerton Lunter
Genetic test

Patient Sample → Sequencing → Analysis → Interpretation → Clinical Report
Traditional interpretation

1. Slow, laborious highly intensive analysis of each variant to decide if pathogenic.
2. Handled by specialised team.
4. Often final/interim classification was ‘uncertain’.
5. Often testing unaffected individuals - no immediate clinical management implications.
Interpretation requirements

1. Intelligible and usable by non-expert/patients
2. High-throughput + large volume
3. Fast turnaround
4. Avoidance of potential harms at individual and societal level
Academic variant classification

V6
V7
V2
V5
V1
V8
V4
V9
V10
V3
V10
V1
V2
V3
V4

definitely pathogenic
likely pathogenic
Uncertain (VUS)
likely not pathogenic
not pathogenic

Plon et al Hum Mutat 2008 29:1282-91

?? Clinical Action
Academic variant classification

Plon et al Hum Mutat 2008 29:1282-91
BRCA genes are very variable in normal population

- 831 UK population tested with TruSight Cancer panel
- 4 pathogenic BRCA mutations (all truncating)

<table>
<thead>
<tr>
<th>All BRCA variants</th>
<th>Missense BRCA variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>100%</td>
</tr>
<tr>
<td>up to 5%</td>
<td>44%</td>
</tr>
<tr>
<td>up to 1%</td>
<td>27%</td>
</tr>
<tr>
<td>up to 0.1%</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>100%</td>
</tr>
<tr>
<td>up to 5%</td>
<td>37%</td>
</tr>
<tr>
<td>up to 1%</td>
<td>18%</td>
</tr>
<tr>
<td>up to 0.1%</td>
<td>9%</td>
</tr>
</tbody>
</table>

>95% non-truncating BRCA variants are not pathogenic
Potential harms of mismanagement of VUS

- Cancer surveillance for index and family
- Risk-reducing surgery
- Neonatal and prenatal testing / interventions

High potential for harm and financial burdens to health services
Clinical variant management
Clinical variant management

Action 3

Action 2

Action 1

Manage as not clinically relevant
Clinical variant management

Action 3

Action 2

V1, V2, V3, V5, V6, V7, V8, V9, V10

Manage as not clinically relevant
Clinical variant management

Fulfil explicit criteria

Manage as not clinically relevant
BRCA Clinical variant management

Pathogenic Mutation

Variant requiring evaluation (VRE)

Variant

Manage as clinically relevant (16%)
- V8

Specific evaluation within 3 months (<0.2%)
- V1
- V5
- V3
- V2
- V6
- V7
- V10
- V9
- V4

Manage as not clinically relevant (74%)

Pipeline takes ~13 working days for 96-192 samples
 Genetic Testing

Patient Sample → Sequencing → Analysis → Interpretation → Clinical Report
How can we implement large scale, routine testing?
Medical genetics in people with disease vs Predictive genetics in healthy individuals
Mainstreaming ‘Oncogenetic’ Model

- **Medical testing** (i.e. in cancer patients) through ‘trained’ cancer team.
  - All test results interpreted by Genetics
  - Mutation – all sent Genetics appointment
  - No Mutation – likely no extra Genetics input needed.
- **Testing in unaffecteds** done through Genetics.
Started with BRCA testing in ovarian cancer

>15% ovarian cancer due to germline mutations.

- Major impact on cancer management
- Major opportunity for cancer prevention.
- Current eligibility complex and performs poorly.
- Inequity compared to breast cancer.
- Renewed interest because of PARP inhibitors.
ACTIONS by trained Cancer Team member
1. Information sheet (MS IS1) given to patient.
2. BRCA testing discussed.
3. Consent obtained.
4. Blood and request form sent to lab.

Genetics review and interpret results

ACTIONS by Genetics
1. Result sent to patient and cancer team.
2. Information sheet (MS IS2/IS3/IS4) sent to patient.
3. Appointment sent if mutation identified.

Patient with non-mucinous ovarian cancer

More discussion required

Refer to Genetics

All resources available at www.mcgprogramme.com
Simple training for non-geneticists

• Takes ~30 mins
  ➢ 4 short e-learning modules on YouTube
  ➢ Read documentation
  ➢ Complete checklist
• Receive certificate.

www.mcgprogramme.com/BRCAtesting
207 women tested

133 impacted management

33 BRCA mutation (16%)

Only 10 met current testing criteria (but none had been referred)

Patient impact
Chemo treatment – PARP
Breast cancer risk management

Family impact
>80 relatives informed
39 have been tested

Ovarian cancer routine gene testing
Ovarian cancer routine gene testing

207 women tested

133 impacted management

33 BRCA mutation (16%)

EVERY patient offered test wanted it
Breast cancer BRCA mainstreaming

July 2013
- Bilateral breast cancer, both <50yrs
- Triple negative breast cancer <50yrs
- Breast cancer + ovarian cancer - any age

Feb 2015
- Breast cancer <40 years
- Bilateral breast cancer - both <60 years
- Triple-negative breast cancer - any age
- Breast cancer + ovarian cancer - any age
- Male breast cancer - any age

~10% threshold
- 54 patients
- 11 mutation positive
- 20% mutation rate

~5% threshold
## Feedback

<table>
<thead>
<tr>
<th>Patient feedback</th>
<th>Clinician feedback</th>
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<tbody>
<tr>
<td>• 100% pleased had test.</td>
<td>• 100%: I welcome the opportunity to carry out BRCA gene testing for cancer patients through oncology appointments.</td>
</tr>
<tr>
<td>• 100% happy to have test at oncology appt.</td>
<td>• 100%: I feel confident to consent a patient for a BRCA gene test; and inform patients of their results.</td>
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<td>• 98% understood may have implications for themselves and their families.</td>
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Effective and Efficient

Cost savings
4x throughput at ¼ cost

Time savings
<4 wks vs 21 wks

Many units are adopting all / parts of process in UK / Europe / USA
Genetic Testing

Patient Sample → Sequencing → Analysis → Interpretation → Clinical Report

- Large-scale (96-192/wk)
- Fast (3 weeks)
- Affordable (£300)
Summary

Delivering large-scale, high-throughput genetic testing in breast cancer patients is achievable and can result in important clinical and economic benefits.

It requires integration of multiple disciplines and an appetite for change.
Acknowledgements

>200 people are involved in the MCG programme
Nazneen Rahman (programme director)
Daniel Riddell (programme manager)
Shazia Mahamdallie, Elise Ruark, Angela George, Helen Hanson, Clare Turnbull, Ingrid Slade, Zoe Kemp
TGLclinical: Vicky Cloke, Sheila Seal, Ann Strydom
RM Genetics, Gynae and Breast Units
UK Cancer Genetics Consultation Group
WTCHG - Márton Münz, Anna Fowler, Gerton Lunter