Genetics Quality and Accreditation workshop

External Quality Assurance in Genetics Laboratories

Farrah Khawaja
Deputy Scheme Director
UK NEQAS for Molecular Genetics
The Royal Infirmary of Edinburgh
Monogenic diseases EQAs
New born screening EQAs
Pre-implantation Genetic Diagnosis
Non-invasive prenatal testing pilot
Molecular Rapid Aneuploidy testing EQA
100K Genomes project EQAs
Next Generation Sequencing pilot
Molecular Pathology
Tumour Assessment
Training/Competency
<table>
<thead>
<tr>
<th>Monogenic diseases EQAs</th>
<th>Frequency: Annually</th>
<th>No. of EQAs: 28 inherited disorders</th>
<th>Assessment: Genotyping, Interpretation, Clerical Accuracy</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>New born screening EQAs</th>
<th>Frequency: Quarterly</th>
<th>No. of EQAs: - CF, - MCAAD</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Assessment: Genotyping only</td>
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</table>
PGD for Monogenic Disorders – 2017: CF

Two Stage EQA
- Stage 1 – Feasibility study testing DNA samples
- Stage 2 – Single cell testing/embryo testing

PGD Blastomere/Trophectoderm Array/NGS In Collaboration with CEQAS
- Aneuploidy
- Chromosome rearrangement
- Polar Body
NIPT for aneuploidies testing
Chromosomes 13, 18 and 21
In Collaboration with CEQAS and EMQN

Frequency: Annually
No. of EQAs: 1 (pilot)
Assessment: Genotyping Only

Non-invasive prenatal testing pilot
Rapid aneuploidy testing
Chromosomes 13, 18 and 21
In Collaboration with CEQAS

Frequency: Annually
No. of EQAs: 1
Assessment: Genotyping
Interpretation
Clerical Accuracy
**Molecular Pathology**

**Frequency:** Annually  
**No. of EQAs:** 6

**Assessment:** Genotyping & Interpretation  
- **MSI testing** (inc $BRAF$ & $MLH1$ promoter methylation)  
- **Sarcoma testing** (In Collaboration with CEQAS)  
- **BRCA testing in ovarian cancer** – somatic & germline (pilot)  
  (In Collaboration with EMQN)

**Frequency:** Annually  
**No. of EQAs:** 1

**Assessment:** Genotyping only  
- **Gastro-Intestinal Stromal Tumours (GIST)**  
- **Molecular Tissue identification** (pilot)  
- **Additional lung biomarkers** ($ROS1$, $RET$ and $MET$)

**NEW**

**Frequency:** Annually  
**No. of EQAs:** 1

**Assessment:** Genotyping only  
IQNPath pilot with EMQN, AIOM, ESP
TECHNICAL EQAS

Next Generation Sequencing pilot

Frequency: Annually
No. of EQAs: - Germline
- Somatic
(In Collaboration with EMQN)

100K Genomes project EQAs

Frequency: Annually
No. of EQAs: - DNA extraction from Blood
- DNA extraction from FFPE
- DNA extraction from FF tissue (pilot)
- DNA extraction from Saliva (pilot)
- DNA quality measurement (pilot)
5.1.6 Competence assessment

Following appropriate training, the laboratory shall assess the competence of each person to perform assigned managerial or technical tasks according to established criteria.

Reassessment shall take place at regular intervals. Retraining shall occur when necessary.

NOTE 1 Competence of laboratory staff can be assessed by using any combination or all of the following approaches under the same conditions as the general working environment:

a) direct observation of routine work processes and procedures, including all applicable safety practices;

b) direct observation of equipment maintenance and function checks;

c) monitoring the recording and reporting of examination results;

d) review of work records;

e) assessment of problem solving skills;

f) examination of specially provided samples, such as previously examined samples, interlaboratory comparison materials, or split samples.

NOTE 2 Competency assessment for professional judgment should be designed as specific and fit for purpose.
Histopathology tissue assessment for molecular testing

- Range of tissue types covered
- Mark regions of tumour appropriate for macrodissection for molecular testing
- Estimate the cellularity & percentage of neoplastic nuclei across the slide image and within the annotated region
- Collaborating with PathXL
- NHS England funded for NHS Genomic Medicine Centres
Tissue EQA Genetics Training Assessment and Competency Tool

Genomics Education Programme
Sample Reception

Report authorisation

Data analysis

Duty Scientist

GTACT EQA
EQA

Laboratory based

Clinician based

Interactive

Click on in tray to view samples

…Or the door to leave
GOTACT

EQA Sample Reception Module

Open Package  Reject Referral  Close

3 ml

SAMPLE

Surname  First Name  Address

Nutmell  Annabella

DATE OF BIRTH 13/12/2001

SEX Female

PATIENT ADDRESS & POSTCODE
164 Thames Street
Kilmarnock

KA9 8KD

GP NAME & ADDRESS

NHS / PRIVATE

CCG CODE

REFERRING CONSULTANT
Dr. Donavan

ADDRESS FOR REPORT

CONTACT NUMBER

MOLECULAR GENETIC TEST (EDTA):

Specify disease / gene test(s) and provide any relevant family history:
SMA

DNA STORAGE ONLY

DIAGNOSTIC TEST

CARRIER TEST

PREDICTIVE TEST

NIPD

UK NEQAS
Molecular Genetics
- Recognition of correct test
- Assigning appropriate priority
Referral ID: 192475

Patient Details  Sample Details  Test Results  Reporting

Test Results

- **Gene**: CRTAP
- **Transcript**: LRG_461, NM_006371.4
- **cDNA Level**: c.55_70del
- **gDNA Level**: Chr11:G

**Report**

This patient is likely to have a pathogenic novel c.55_70del, p.(Cys19Glyfs*18) frameshift variant in exon 1 of the CRTAP gene, and an apparent homozygous state.

This result is consistent with a diagnosis of Osteogenesis imperfecta type VII (OMIM #810682).

Testing this patient's parents for this variant is recommended to confirm the homozygosity of this variant in the fetus and rule out other large rearrangements of the CRTAP gene as the cause of the disease. This will also confirm their carrier status and determine recurrence risks.

Significant maternal cell contamination has been excluded by qPCR analysis.

**Literature**

- **CRTAP c.55_70del (homozygous)**
  1. No evidence for c.55_70del variant reported in literature or variant databases including LOVD (https://variation.lifecode.org/home.php?select_db=CRTAP)
  2. Phenotype of fetus is consistent with CRTAP variants being causal variants in CRTAP cause AR Osteogenesis imperfecta type VII (OMIM #810682)
  3. c.55_70del is consistent with the reported spectrum of pathogenic variants for this gene, most reported cases are null mutations (OMIM #810682). Most null cases are lethal in the perinatal period or within the first year of life, Valli et al. (2012).

**ExAC Database frequency**

ALL 0.0057% AFR:0% AMR:0% EAS:0% SAS:0.021% NFE:0% FIN:0% OTH:0% (29226 cases in Asians, no homozygotes)

**Classification**

Class 5: Clearly pathogenic
EQA Variant Assessment Module

Referral > Kyle, Barnes

- **Patient**: Kyle, Barnes
- **Male**: Yes
- **DOB**: 1992
- **NHS No.**: 122423455
- **Hospital Number**: A32587

**Notes**
Kyle Barnes (dob 15/02/1992) is presenting with pulmonary stenosis and has short stature and a webbed neck. His mother also appears to have features of Noonan syndrome and a local Consultant Clinical Geneticist has requested testing Kyle for Noonan Syndrome.

**Tests Completed**

- **Test**: NOS RASMAPK
- **Date**: 29/2/2017

**Referral : Kyle, Barnes > Test : RASMAPK**

- **Patient**: Kyle, Barnes
- **Test**: NOS RASMAPK
- **Completed**: 29/2/2017

**Gene**

- **PTPN11 (LRG_614t1): c.922A>G**

**Classification**

- **Class 4 - Likely to be pathogenic**

**Evidence**

- Enter the evidence for the above classification here....

**PARP Inhibitor Treatment**

- **Yes**
- **No**
EQA Participation Dashboard

- Flexibility to complete scenarios at a later date

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<th>Scenario</th>
<th>Started</th>
<th>Completed</th>
<th>Outcome</th>
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Demonstrate competency

... or identify any errors

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Line manager can view results for all TACT users

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</table>
Line managers can view all details entered by individuals. The visual data field can be used to view the request card and label for each referral given in a scenario.
- Leave individual feedback
- Perform periodic review of staff
- Override results based on local practice
Participant numbers 2016

Number of EQA Schemes

Number of Laboratories

Number of Participations
Scheme Activity 2016

68 Countries

<table>
<thead>
<tr>
<th>Continent</th>
<th>No. of Labs</th>
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<tbody>
<tr>
<td>Europe - UK</td>
<td>102</td>
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<tr>
<td>Europe - Non-UK</td>
<td>288</td>
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<tr>
<td>Africa</td>
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<td>Asia</td>
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<td>Australasia</td>
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<td>South America</td>
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Number of Labs per Continent

- Europe - UK: 18%
- Europe - Non-UK: 52%
- Africa: 7%
- Asia: 11%
- Australasia: 3%
- North America: 6%
- South America: 7%
Participant meetings 2017

1. Participants’ meeting 2017 – May at ESHG - NIPT, Copenhagen, Denmark

Measuring the quality of non-invasive prenatal testing

EQA providers Participants’ meeting

Monday 29th May, 2017 at 11:00-13:00h
ESHG Conference 2017, Bella Centre, Copenhagen

Agenda

Chair – Dr Erik Sistermans

11:00 – 11:20h NIPT for aneuploidies pilot EQA results
Dr Sandi Deans, Director, UK NEQAS for Molecular Genetics

11:20 – 11:35h NIPT laboratory survey findings
Dr Ros Hastings, Director, CEQAS

11:35 – 11:50h Recommendations for reporting NIPT for aneuploidies results
Nicola Wolstenholme, Deputy Director, EMQN

11:50 – 12:10h TRIDENT 1 and 2
Dr Erik Sistermans, VU University Medical Center, Amsterdam, The Netherlands

12:10 – 12:30h Development of NIPD for monogenic disorders
Natalie Chandler, Great Ormond Street Hospital, London

12:30 – 13:00h The Great Debate:
NIPT should always include microdeletions and rare trisomies
For: Prof Joris Vermeesch, KU Leuven, Belgium
Against: Dr Heleen Schuring-Blim, UMC Utrecht, The Netherlands

Lunch and refreshments will be provided
Participant meetings 2017

1. Participants’ meeting 2017 – May at ESHG - NIPT, Copenhagen, Denmark

2. UK NEQAS for Molecular Genetics Participants’ meeting 2017 – June at ACGS, Birmingham
Acknowledgements

- The development of this training assessment and competency tool has been partly supported by a grant from Health Education England.

Director: Dr Sandi Deans
UK NEQAS for Molecular Genetics Team
Specialist Advisory Groups
What do you want?