EMQN
The European Molecular Genetics Quality Network

IQNPath proposal for a pilot EQA scheme for fusion genes testing

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Role of Fusions in Cancer

History: Diagnosis and prognosis

- Philadelphia chromosome in CML t(9:22) *BCR-ABL1*
- Ewing's sarcoma t(11;22) *EWSR1-FLI1*

2019: Era of Targeted and Personalised treatments

- 'Druggable' tumour fusions e.g. *TMPRSS2*, *RET*, *FGFR3*, *ALK*, and *ESR1* in 6.0% of cases in a study of 9,624 tumours across 33 cancer types [(1)]
- Drive the development of 16.5% of all cancer cases (sole driver >1%) [(1)].
  - 8.3% both driver mutations and driver fusion events
  - 6.4% both mutations and fusions in driver genes
  - 1.8% driver fusions only
- *Specificity to cancer cells = excellent targets for molecular therapy* [(2)]

Clinical Relevance of Gene Fusions

Lung cancer:

- Three rearranged tyrosine kinase (TK)s are found in ~5-10% of non small cell lung cancers
  - *ALK (3-7)%*
  - *ROS1 (1-2)%*
  - *RET (0.7-2%)*[3].
- Spectrum of lung mutations: almost 30% of patients carrying an activated oncogene show the fusion of a tyrosine kinase to an heterologous gene[3].
- Tyrosine kinase inhibition therapies are licensed e.g. crizotinib in EML4-ALK translocations

Colorectal Cancer:

- Historically believed to be rare events
- Primary colon cancer 2.5% of specimens harbour a relevant gene fusion (kinase fusions 1.8%) [8]
- In CRC samples 8.8% samples had fusion rearrangements [9]

NTRK gene fusions (*NTRK1-3)*

- Encode tropomyosin receptor kinases Trk A, B and C
- Seen across many tumour types [4]
- High response rates (>75%) irrespective of tumour type reported first-generation TRK inhibitors e.g. larotrectinib or entrectinib [5]
- Frequency of NTRK gene fusions in NSCLC of 0.23% [5] to 3% [6]
- Frequency of NTRK gene fusions in colorectal cancer may have been under-reported in the absence of treatments

FGFR fusions *(FGFR1-3)*

- Transmembrane kinase proteins
- Fusions reported in bladder , urothelial cancer, glioblastoma, gallbladder, cervical, etc.
- *FGFR* aberrations found in 7.1% of cancers (multiple cancers),
  - gene amplification (66%), mutations (26%) rearrangements (8%). [12]
- Erdafitinib has been licensed (FDA) for treatment of urothelial cancer

MET Exon 14 skipping

- Not a fusion event but detected using analysis of RNA
- Predicts response to *MET* inhibitors
- 3% - 5.6% NSCLC [10][11]
  - Both adenocarcinoma and Squamous cell carcinoma

Proposal

- IQNPath will facilitate a single IQNPath badged pilot EQA scheme for fusion gene testing (comprising of two EQA distributions), run independently by each provider.

Role of IQNPath

- Facilitation of pilot schemes:
  - Harmonised EQA scheme process
  - Agreed timetable
  - Allow EQA providers participating in the pilot and complying with it's code of practice to use IQNPath logo

Scheme Organisation

Process

- Two rounds of pilot EQAs to develop a model
  - Assess suitable material and suppliers
  - Harmonised process/practice

Round 1: genotyping only

Round 2: genotyping, interpretaion and clerical accuracy

- At the end of the pilot stages: EQA providers deliver their own fully costed and financially sustainable independent schemes

Prior to commencement

- EQA providers agree a common procedure for both pilots
  - Deviations must be agreed by all providers in advance

Project Management

- A part-time project manager (PM) to co-ordinate the pilots and ensure timelines

Expression of Interest

- Currently: EMQN, GenQA, AIOM, ESP – call to other IQNPath members

Scheme Organisation

Participants

Pilot 1: Maximum 10 for each EQA provider

Pilot 2: Unlimited number from each EQA provider.

- Measures to ensure that there is no duplication of laboratories
- Participants should be directed to National providers preferentially in the pilots but are free to choose in later schemes
- Pilot participation data to be shared to ensure transparency/oversight

Scope

Target

- RNA testing for fusion products in FFPE (artificial reference materials)

Gene fusions including:

- *ALK*
- *ROS-1*
- *RET*
- *NTRK1-3*
- *FGFR1-3*

Additional RNA based testing

- MET exon-14 skipping

Financial Considerations

Marketing

- Pilot EQAs should be marketed by EQA providers and IQNPath
- Project manager will co-ordinate
- Common agreed text

Funding of Pilots

- Materials will be expensive
  - Common set of materials / existing tender process
- Free for participants
- Sponsorship for R & D, EQA provider costs and participation
  - Estimated 500-600 Euro per participant

Timelines and Planning

Action	Deadline
Survey laboratories (establish practice)	30.07.2019
Establish maximum number of samples	31.08.2019
Define Material Spec/complete tender process	31.10.2019
Place order for EQA materials	30.11.2019
Receipt of EQA materials	30.05.2020
Completion of EQA material validation	30.08.2020
Sample distribution	15.09.2020
Reporting deadline	31.10.2020
Publication of validated results	30.11.2020
Completion of assessment / publication of results / summary scheme report	30.11.2020
Publication of final results	30.11.2020

2019

- Planning to start in 2019 including identification of sponsors
- EQA material distribution in **September 2020**

Samples

Manufacturing

Commercial Reference Materials

- Advantages of commercially available reference materials
  - Stability and homogeneity
  - Sufficient supply for all providers

Tender Process

- IQNPath should co-ordinate a list materials/manufacturers
- Planning meeting to develop the genotypes/specifications

Validation

Model

- Use existing model for trial validation prior to pilot (cfDNA pilot)
- Methodologies relevant to clinical practice
- Experienced validation laboratories
  - Choosing expert centres and differing methodologies
- Collecting information on:
  - Lab quality metrics & experience
  - RNA extraction methodology and results
  - test methodology and results

Documentation

General

- Common documentation for marketing, scheme instructions, referral information and overall summary scheme report
- Each provider can also produce a local feedback report to their own format
- National scheme providers may translate documents into their own language

Assessment

General

- Each provider independently manages and assesses results using harmonised criteria
- IQNPath co-ordinates training of all assessors e.g. WebEx
  - A small number of labs are assessed by all providers for harmonisation
- Agreed timetable

Pilots

First pilot

- Genotyping only with no appeals

Second pilot

- Genotyping, clinical interpretation and clerical accuracy
- Poor performance applied **only** to genotyping
- Includes a appeal process

Dissemination

Modes of dissemination

Conferences

- Results from both pilots should be disseminated widely

Journals

- Results of both pilots to be published
  - Authorship to be agreed upfront
  - Substantive contribution to the paper and its review is required for authorship

Intellectual property

- shared equally amongst all the participant EQAs

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EMQN Team

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EMQN Scientific and Administrative teams

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Pharma

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