**Application to be an additional provider for existing test on the NHS Directory of Molecular Genetic Testing**

**Additional Provider form**

**Disease**: Cystic Fibrosis (CF)  (in symptomatic child)

**Gene**: CFTR

### Test – Disease – Population Triad

<table>
<thead>
<tr>
<th>Disease – name and description (please provide any alternative names you wish listed)</th>
<th>Cystic Fibrosis (CF) (in a symptomatic child)</th>
</tr>
</thead>
</table>
| **(A)-Testing Criteria** | Clinical suspicion of CF:  
  (ie. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus) |
|  | Testing criteria: Must have not-normal sweat test, performed in a recognized experienced test centre /laboratory.  
  (see Target Population for Testing Criteria) |

| OMIM number for disease | 219700 |

| Gene – name and description (please provide any alternative names you wish listed) | Cystic Fibrosis Transmembrane Conductance Regulator; CFTR |

| OMIM number for Gene | 602421 |

| Mutational spectrum for which you test | 29 or 33 – mutation kit scan, (and intron 8 polythymidine repeat : 5T/7T/9T polymorphism)  
  Full sequencing if only single mutation found, or if no mutation but clinically unequivocally CF (see below). |

| Technical Method(s) | Prior Clinical testing must include:  
  - Sweat test  
  29 or 33 – CFTR mutation kit  
  Intron 8 polythymidine repeat (5T/7T/9T) polymorphism  
  CFTR sequencing: if -  
  - only one common mutation found  
  OR: clinically unequivocally CF (sweat Na+ & Cl- both >60mM), but no mutation found,  
  OR: not-normal sweat test (ie. sweat Cl- >40mM with sufficient sweat obtained (>30mM in infants)), performed in a recognized experienced test centre /laboratory but no mutation found, AND either parental consanguinity present, or from ethnic background with much higher proportion of ‘rarer’ mutations. |

| Validation Process | Note please explain how this test has been validated for use in your laboratory |
How many reports have you produced for this test?
NB please give the number of mutation positive/negative samples you have reported

For how long have you been providing this service?

Is there specialised local clinical/research expertise for this disease?
Yes  No  Please provide details

Are you testing for other genes/diseases closely allied to this one? Please give details
Other CFTR-related disorders
- Adult CT scan-proven bronchiectasis
- chronic pancreatitis
- CBAVD
Routine CFTR mutation scanning of sperm /egg donors

Your Activity
How many tests do you (intend to) provide annually in your laboratory?

Epidemiology

Estimated prevalence of disease in the general UK population
Please identify the information on which this is based

CF Incidence : approx. 1 in 2300 births in UK;
- but differs greatly in different racial groups.

Estimated gene frequency
(Carrier frequency or allele frequency)
Please identify the information on which this is based

<table>
<thead>
<tr>
<th>Carrier frequency: racial-origin-dependent</th>
<th>% mutns detected</th>
<th>df508</th>
<th>4-mut.kit</th>
<th>29/33 mut.kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 24 in Caucasian English</td>
<td>75 %</td>
<td>81 %</td>
<td>90 %</td>
<td></td>
</tr>
<tr>
<td>1 in 60 in African-American</td>
<td>48 %</td>
<td></td>
<td>50 %</td>
<td></td>
</tr>
<tr>
<td>1 in 50 in UK Asian</td>
<td>28 %</td>
<td>28 %</td>
<td>29 %</td>
<td></td>
</tr>
<tr>
<td>1 in 23 in S.Europe</td>
<td>50 %</td>
<td>58 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 in 90 in non-specified Asian</td>
<td></td>
<td>&lt;30 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 in 280 in Japanese Asian</td>
<td></td>
<td>&lt;57 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 in 45 in Mexico</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 in 23 in Ashkenazi Jewish</td>
<td>43 %</td>
<td></td>
<td>97 % *</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*(W1282X = 37%)</td>
<td></td>
</tr>
</tbody>
</table>

Target Population

The essential clinical or family history features defining the target population must be described.

(C)-Testing Criteria

Child in whom there is a clinical suspicion for CF
(eg. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus)

AND : A 'not normal' sweat test performed in a recognized experienced test centre /laboratory (ie. sweat Cl- >40mM with sufficient sweat obtained, (>30mM in infants))

OR: Occurrence of an additional urgent prenatal situation for the parents or for a close relative, but urgent sweat testing not accessible.
### Estimated prevalence of disease in the target population

| High if did not have newborn screening; Lower in those negative on newborn screening (but data not yet known). |

### Test Characteristics

#### Analytical sensitivity and specificity

This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up.

If a number of genes will be tested, please include your testing strategy and data on the expected proportions of positive results for each part of the process.

It may be helpful to include a diagram to illustrate the testing strategy.

#### Testing Strategy:

1. Child in whom there is clinical suspicion for CF
2. Sweat test performed in a recognized experienced centre/laboratory (must be 'not normal' (ie. sweat Cl- >30mM with sufficient sweat obtained),
3. Ethnic origin and any consanguinity noted
4. CFTR 29 or 33 mutation-kit scan
5. Intron 8 polyT repeat (5T/7T/9T) if appropriate
6. CFTR sequencing: if -
   - only one common mutation found
   - OR: clinically unequivocally CF (sweat Na+ & Cl- both >60mM), but no mutation found,
   - OR: not-normal sweat test (performed as above), but no mutation found AND either parental consanguinity present, or from ethnic background with much higher proportion of 'rarer' mutations.

Samples accepted for testing:
- Blood /DNA from child
- Exceptionally, blood /DNA from both parents in lieu of from child

**Test Sensitivity:** This is dependent on racial origin (see Epidemiology section above). For UK Caucasians 29/33 mut. Kit: will detect both mutns. in ~ 81% of CF affecteds; one mutn only in ~ 18%; no mutn in ~ 1 %

**Specificity:** Sequencing / MLPA would be expected to have high sensitivity for detecting 2nd mutation where one is present, but reduced specificity due to novel variants.
Referral Pathway Template –

**TARGET POPULATION**  (Description)
Child in whom there is a clinical suspicion for CF: (eg. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus)

AND: A ‘not normal’ sweat test performed in a recognized experienced test centre/laboratory (ie. sweat Cl- >40mM with sufficient sweat obtained, (>30mM in infants))

OR: Occurrence of an additional urgent prenatal situation for the parents or for a close relative, but urgent sweat testing not accessible.

**WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?**
Consultant Paediatrician or Neonatologist
Respiratory Paediatrician or Paediatric Gastroenterologist
Paediatric CF specialist
Clinical Geneticist

**PLEASE PROVIDE DETAILS OF HOW REFERRALS WILL BE ASSESSED FOR APPROPRIATENESS?**
Laboratory performing test must see evidence on the referral form that the clinical details match the test criteria (ie. indication of sweat test result).

**HOW MANY TESTS DO YOU PERFORM ANNUALLY?**
UKGTN Testing criteria for disease:

Name of Disease(s): Cystic Fibrosis (CF) in a symptomatic child (219700)
Name of gene(s): Cystic Fibrosis Transmembrane Conductance Regulator; CFTR (602421)

Patient name: Date of birth:
Patient postcode: NHS number:
Name of referrer:
Title/Position:
Lab ID:

Referrals will only be accepted from one of the following:

<table>
<thead>
<tr>
<th>Referrer</th>
<th>Tick if this refers to you.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatrician or Neonatologist</td>
<td></td>
</tr>
<tr>
<td>Respiratory Paed. or Paed.Gastroenterol.</td>
<td></td>
</tr>
<tr>
<td>Paediatric CF specialist</td>
<td></td>
</tr>
<tr>
<td>Clinical Geneticist</td>
<td></td>
</tr>
</tbody>
</table>

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Tick if patient meets criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child with clinical suspension of CF (eg. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus)</td>
<td></td>
</tr>
<tr>
<td><strong>AND</strong>: A 'not normal' sweat test performed in a recognized experienced test centre / laboratory (ie. sweat Cl- &gt;40mM with sufficient sweat obtained, (&gt;30mM in infants)),</td>
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<tr>
<td><strong>OR</strong>: An additional urgent prenatal situation for the parents or for a close relative, but urgent sweat testing not accessible.</td>
<td></td>
</tr>
</tbody>
</table>

If the sample does not fulfil these criteria and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.