### Proposal form for the evaluation of a genetic test for NHS Service Gene Dossier

**Test – Disease – Population Triad**

<table>
<thead>
<tr>
<th>Disease – name and description (please provide any alternative names you wish listed)</th>
<th>Name: Pulmonary Surfactant Metabolism Dysfunction type 2 (SMDP2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative Names:</strong></td>
<td></td>
</tr>
<tr>
<td>- Interstitial lung disease due to surfactant protein C deficiency</td>
<td></td>
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<tr>
<td>- Desquamative interstitial pneumonitis due to surfactant protein C deficiency</td>
<td></td>
</tr>
<tr>
<td>- Pulmonary alveolar proteinosis due to surfactant protein C deficiency</td>
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<tr>
<td>- Respiratory distress syndrome</td>
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<tr>
<td><strong>Description:</strong></td>
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<tr>
<td>SMDP2 is a rare autosomal dominant disease associated with progressive respiratory insufficiency and lung disease with a variable clinical course. Pulmonary surfactant metabolism disorders are associated with various pathologic entities, including pulmonary alveolar proteinosis (PAP), desquamative interstitial pneumonitis (DIP), or cellular non-specific interstitial pneumonitis (NSIP). SMDP2 is progressive and has a variable clinical course with patients who survive to adulthood manifesting features of pulmonary fibrosis. The congenital pulmonary surfactant metabolism dysfunction disorders are distinct from respiratory distress syndrome (RDS; 267450), which affects preterm infants and is associated with the pathologic finding of hyaline membrane disease.</td>
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</tr>
</tbody>
</table>

| OMIM number for disease | #610913 |

<table>
<thead>
<tr>
<th>Gene – name and description (please provide any alternative names you wish listed)</th>
<th>Name: Pulmonary-associated Surfactant Protein C (SFTPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternative Names:</strong></td>
<td></td>
</tr>
<tr>
<td>- Pulmonary surfactant - associated protein 2 (SFTP2)</td>
<td></td>
</tr>
<tr>
<td>- Pulmonary surfactant apoprotein PSP-C (SPC PSP-C)</td>
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<tr>
<td>- Surfactant Proteolipid SPL-pVal</td>
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<tr>
<td>- Pulmonary surfactant protein SP5</td>
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<tr>
<td><strong>Description:</strong></td>
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<tr>
<td>The SFTPC gene encodes pulmonary-associated surfactant protein C (SPC). This protein is an extremely hydrophobic surfactant protein produced exclusively by type II alveolar epithelial cells in the lung. SPC forms part of the pulmonary surfactant, a lipid-rich material that prevents lung collapse by lowering surface tension at the air-liquid interface in the alveoli of the lung and increases pulmonary compliance. Surfactant protein C is routed with surfactant protein B precursor protein to multi-vesicular bodies within type II alveolar cells, where both are processed and packaged into lamellar bodies for secretion into the alveoli. The pathophysiology of the disorder is postulated to involve intracellular accumulation of a structurally defective SPC protein. The function of SPC can be modified by variants in ABCA3. The gene consists of five coding exons and one non-coding exon spanning 3.5 kb encoding a 197 precursor protein, which is processed to a 35 amino acid mature protein whose structure is primarily of a membrane-spanning alpha-helical hydrophobic domain. Mutations are generally inherited in an autosomal dominant manner and are partially penetrant.</td>
<td></td>
</tr>
<tr>
<td><strong>OMIM number for Gene</strong></td>
<td><em>178620</em></td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td><strong>Mutational spectrum for which you test</strong></td>
<td>Missense, nonsense and small insertion and deletion mutations identified throughout the gene.</td>
</tr>
</tbody>
</table>
| **Technical Method(s)** | Direct sequencing of all coding exons (5) and exon/intron boundaries  
Family mutations: PCR and restriction enzyme digest or sequencing |
| **Validation Process** | Sequencing is a standard analytical method used in the laboratory for a range of diagnostic services requiring mutation detection. The laboratory participates in external quality assessment for sequence analysis. |
| **Are you providing this test already? If yes, how many reports have you produced?** | Yes  
20 x full screen – 5 individuals with mutations identified  
17 x family mutation – 9 carriers identified |
| **For how long have you been providing this service?** | Full screen available end of 2006 |
| **Is there specialised local clinical/research expertise for this disease?** | Yes √ No  
**Please provide details**  
Dr Quen Mok  
Consultant Intensivist,  
Paediatric Intensive Care Unit, Great Ormond Street Hospital,  
London WC1N 3JH |
| **Are you testing for other genes/diseases closely allied to this one? Please give details** | Yes  
SMDP2 is offered as part of our service for inborn errors of pulmonary surfactant metabolism. The laboratory also offers testing for;  
Pulmonary Surfactant Metabolism Dysfunction type 1 (OMIM #265120) due to mutations in Pulmonary-associated Surfactant protein B (SFTPB) gene.  
Pulmonary Surfactant Metabolism Dysfunction type 3 (OMIM #610921) due to mutations in ATP-binding cassette, subfamily A, member 3 (ABCA3) gene. |
| **Your Activity** | Over the last three years the number of referrals has increased;  
2006  3 full screens  
2007  13 full screens  
2008  5 full screens to date  
We therefore expect to provide around 20-30 referrals annually. |
| **Based on experience how many tests will be required nationally (UK)?** | We have been accepting samples from around the UK for the last 2 years and the above figures are based on this. Therefore we expect a national service of around 20-30 referrals annually. Additional referrals are received from outside the UK. |
### Epidemiology

| **Estimated prevalence of disease in the general UK population** | Unknown – rare  
The incidence of all forms of interstitial lung disease in the UK was estimated at 1 in 3.6 million. 46 cases were identified over a three-year period 1995-1998. 76% of cases present in the first year of life and SMPD accounts for a small fraction of these cases.  
| **Estimated gene frequency**  
*(Carrier frequency or allele frequency)* | SFTPB is estimated to have a carrier frequency of 1/1000-1/3,000  
| **Estimated penetrance**  
Please identify the information on which this is based | SMNP2 is autosomal dominant but is not fully penetrant. Patients can present with symptoms of Interstitial lung disease in adulthood or they may remain asymptomatic. There are several case reports in the literature of kindred with a severely affected index case and other family members with late onset disease. It is estimated that 54.5% mutations in SFTPC are de novo (see review by Hamvas A. Inherited surfactant protein-B deficiency and surfactant protein-C deficiency associated disease: clinical features and evaluation. *Semin Perinatol.* (2006) 30(6): 316-26).  
| **Target Population**  
The essential clinical or family history features defining the target population must be described.  
(C)-Testing Criteria | Testing will be offered to patients presenting with symptoms as neonates and infants or parents of a clinically suspected neonatal case where limited or no DNA is available from the index case.  
Completion of our proforma will indicate the most relevant cases. |
| **Estimated prevalence of disease in the target population** | Of the referrals received to date with completed proformas (see above section); 5 out of 21 were found to have a mutation. |
**Intended Use (Please use the questions in Annex A to inform your answers)**

<table>
<thead>
<tr>
<th>Please tick the relevant clinical purpose of testing</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Prognosis &amp; Management</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Presymptomatic testing</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Risk Assessment</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
## 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.

Direct sequencing has a high sensitivity in this laboratory. We use big dye chemistry, ABI analysers (3100, 3130XL, 3730) and analysis by eye / Mutation Surveyor software. We participate and perform successfully in EQA programmes for sequence analysis.

The three genes offered as part of the pulmonary surfactant deficiency service; SFTPB, SFTPC and ABCA3 will be tested in order indicated by clinician or as suggested by clinical information provided. If a variant of unknown significance or mutation is identified in SFTPC, then screening of the ABCA3 gene will always be recommended as this has been reported to act as a modifier gene.

### Clinical sensitivity and specificity of test in target population

The **clinical sensitivity** of a test is the probability of a positive test result when disease is known to be present; the **clinical specificity** is the probability of a negative test result when disease is known to be absent. The denominator in this case is the number with the disease (for sensitivity) or the number without disease (for specificity).

The clinical sensitivity is high when there is biopsy information available in the family / family studies and subject to mutation screen results of SFTPB and possibly ABCA3.
Clinical validity (positive and negative predictive value in the target population)

The clinical validity of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical disease or predisposition. It is measured by its positive predictive value (the probability of getting the disease given a positive test) and negative predictive value (the probability of not getting the disease given a negative test). The denominator in this case is the number of people with a positive or a negative test respectively - not the number with or without the disease. The clinical validity may be calculated knowing the sensitivity and the specificity and the prevalence of the disease in the population being studied. Positive and negative predictive values depend critically on the prevalence of the disease in the test population.

The clinical validity is high subject to the reliability of the clinical assessment given the variable penetrance.
| **Clinical utility of test in target population**  
(Please refer to Appendix A) |  
| Testing would primarily be for disease confirmation, carrier testing and prenatal diagnosis.  
Referral criteria include appropriate details on the gestational age and nature of delivery, details of the respiratory disorder, relevant family history, drug interventions, respiratory support and chest X-ray (if available). In consultation with a Consultant Intensivist this data will be used to determine the likely clinical diagnosis and appropriate test pathway.  
Treatment options are very limited but lung transplantation could be an option and has been successful for SFTPB deficiency.  
Confirmation of the diagnosis in a neonate will prevent unnecessary clinical intervention.  
Molecular diagnosis will distinguish mode of inheritance from other causes of SMDP and provide families with opportunities for carrier and prenatal diagnosis. In addition screening of SFTPC may assist in evaluation (risk assessment) of SFTPB and ABCA3 results.  
Due to variability in penetrance and expressivity for some mutations extended family members may also be at risk from disease.  
A negative molecular result in confirmed families would dramatically reduce risk.  
Other diagnostic methods, i.e. lung biopsy can only be carried out post mortem that may be limited by sample availability.  
Diagnosis may assist with the legal, ethical and social decision making process of further intervention. |
| Please provide a full description of the clinical care pathway for those individuals undergoing testing. This should include details of which medical specialties will be able to refer for testing.  
(B)-Testing Criteria  
How will the test add to the management of the patient or alter clinical outcome?  
What impact will this test have on the NHS i.e. by removing the need for alternative management and/or investigations for this clinical population?  
Are there specific ethical, legal or social issues with this test?  
Testing would primarily be for disease confirmation, carrier testing and prenatal diagnosis.  
Referral criteria include appropriate details on the gestational age and nature of delivery, details of the respiratory disorder, relevant family history, drug interventions, respiratory support and chest X-ray (if available). In consultation with a Consultant Intensivist this data will be used to determine the likely clinical diagnosis and appropriate test pathway.  
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Please complete the referral pathway diagram on the following page and the testing criteria form.
Referral Pathway Template –

NOTE: Please use this page as a template. Please expand the test boxes manually as needed.

TARGET POPULATION
(Description)
Patients who present with severe respiratory insufficiency around the time of birth after a full-term gestation period or during early infancy

WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?
Clinical Geneticists and Consultant Intensivists

PLEASE PROVIDE DETAILS OF HOW REFERRALS WILL BE ASSESSED FOR APPROPRIATENESS?
All referring clinicians will be asked to complete a clinical information on the gestational age and nature of delivery, details of the respiratory disorder, relevant family history, drug interventions, respiratory support and chest x-ray (if available). In consultation with a Consultant Intensivist this data will be used to determine the likely clinical diagnosis and appropriate test pathway (order and priority of gene screens particularly if sample is limited)

HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?
20-30
UKGTN Testing criteria:

Name of Disease(s):
SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 2; SMDP2 (610913)

Name of gene(s): surfactant, pulmonary-associated protein C; SFTPC (178620)

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>Clinical Geneticists</td>
<td></td>
</tr>
<tr>
<td>Consultant Intensivists</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 this patient meets criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal respiratory insufficiency of disproportionate severity for advanced gestation, with clinical and X-ray features consistent with pulmonary surfactant deficiency</td>
<td></td>
</tr>
<tr>
<td><strong>AND</strong> No other obvious cause for respiratory distress e.g. no difficult delivery, no infection, not prematurity</td>
<td></td>
</tr>
<tr>
<td>+/- Known F.Hist of pulmonary surfactant deficiency</td>
<td></td>
</tr>
</tbody>
</table>

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.