**Newborn Screening for Cystic Fibrosis incorporating wider genomic sequencing**

**Seeking Stakeholder Views – a Day for Potential Suppliers**

**Introduction**

Thank you for responding to the invitation to a ‘supplier day’ to consider how we might best commission work to explore the opinions of *‘People with a personal experience of cystic fibrosis, CFSPID (cystic fibrosis, screen positive, inconclusive diagnosis) or carrier status’* and *‘Healthcare and other professionals involved in CF screening and follow-up care and support’* in relation to an extended use of genomic testing as part of whole population newborn screening for cystic fibrosis.

A separate public consultation to determine the wider public views will also be undertaken as an extension to the current collaborative public dialogue being undertaken in relation to the use of whole genome sequencing in newborn screening.

**Background to the project**

Newborn screening for cystic fibrosis became part of the national screening programme in 2007. The algorithm used depends upon using immunoreactive trypsin (IRT) as a first line biochemical test. Those babies with an IRT below the 99.5th centile are reported as ‘CF not suspected’. Babies with an IRT above or equal to the 99.5th centile are subject to further tests:

* Firstly by assessing the presence or absence of four common mutations. If the baby has two of these disease causing mutations the baby is referred as ‘CF suspected’.
* If only one mutation is identified from this initial study, testing is undertaken as part of a larger panel of fifty mutations (CF-EU2 panel). If this identifies an additional disease causing mutation the baby is also referred as ‘CF suspected’. Taken together, from the annual total of approximately 650k babies tested in England, 160 babies are referred as CF suspected by these routes. If no additional mutations are identified in the fifty mutation panel then the family are contacted and a second sample obtained for IRT analysis – this happens for approximately 250 babies each year. In 200 of these the second IRT is normal and the family are notified that the baby is likely to be a carrier, in the remaining 50 the IRT is elevated and the baby is referred as ‘CF suspected’.
* If the IRT is particularly high (>99.9th centile – approximately) a second sample is obtained even if no mutations have been identified, this is sometimes referred to as the ‘safety net arm’. Around 50\* such repeat samples are requested each year on this basis. Ten of these turn out to have a lower IRT on repeat and are reported as CF ‘not suspected’, 40\* have an elevated IRT on repeat and are referred as ‘CF suspected’.
* When a baby is reported as ‘CF suspected’ a clinical referral is made to undertake confirmatory testing. This may result in baby being classified as normal (ie a false positive screening test result, the baby is then discharged); CF confirmed (appropriate on-going treatment is then arranged); CF screen positive – inconclusive diagnosis (CFSPID) (while the screening result was positive, the confirmatory tests were equivocal and there is insufficient information to classify the baby as having CF but neither is sufficient clarity to discharge the baby as normal. In these situations some on-going monitoring is arranged.)

As a result of this testing from 650k babies tested each year:

* 250\* are referred as ‘CF suspected’
* 200\* are notified as a possible carrier
* 300\* babies have a repeat test for IRT performed
* 20-30 babies receive a designation as CF screen positive – inconclusive diagnosis (CFSPID)

nb \*These numbers are derived from an extrapolation of the sample study (70k patients) conducted over one year at Sheffield and will need to be verified from the annual data collection statistics.

This algorithm works well but has some disadvantages:

* We report carriers ie one serious mutation identified following an initial raised IRT ​but in which the repeat IRT is normal – around 200 pa.
* We need to perform a significant number of repeat samples which can be distressing for parents and is quite costly to the service – around 300 pa.
* The mutations panels used do not fully reflect the ethnic diversity of the birth population.
* Some babies are designated as CFSPID and this results in uncertainty for the parents and the child as they grow up.

It was speculated that it may be possible to replace the limited panel of mutations following IRT by an extended range of mutations to include the CFTR2 database using next generation sequencing (NGS).   This was trialled this for one year in one centre to include around 70k births.   The NGS analysis scored variants of varying clinical consequence with a score = 1 per allele, and clearly pathogenic mutations = 2 per allele.    Those babies with a combined score of 3 or 4 were referred.

It was found that:

* The NGS protocol was technically feasible at reasonable cost and with an acceptable turn around time.
* The NGS protocol without IRT repeat would result in a small but significant reduction in sensitivity compared with the current protocol.
* This would be mostly but not completely offset by retaining the ‘safety net arm’ (repeat IRT at day 21 for infants with a very high IRT and NGS score <4). The number of infants that go through the safety net would be smaller than with the standard protocol, given the extended gene sequencing involved in the NGS protocol.
* Retaining the safety net would more adequately reflect the non-Caucasian populations with lower F508del incidence and rarer CF causing variants that are not included in the CFTR-2 database
* Carrier recognition would potentially be avoided using the NGS protocol, even if a safety net were retained. The UK protocol has relatively low carrier recognition, however, the advisory board see this as an advantage.
* Including variants of varying clinical consequence in the panel (score = 1) and referring babies with a combined score of 3, results in a significant increase in the recognition of infants with ‘Cystic Fibrosis Screen Positive – Inconclusive Diagnosis’ (CFSPID). The Screening CF advisory board considers this significant increase unacceptable and suggested that avoiding reporting results with scores of 3 as ‘screen positive’ should be considered.​

On that basis the study group recommended that cases with a score of 4 should be referred while maintaining the ‘safety net arm’ when the initial IRT is very high >120µg/L

If that route were followed it would:

* Avoid reporting carriers (around 200 pa nationally).
* Reduce the number of CFSPID cases nationally, potentially this would be zero from the NGS arm, the ‘safety net’ may still identify patients with CFSPID but significantly fewer.
* Reduce the number of repeat IRTs by 70% (from approximately 300 to 50 nationally).
* Miss some cases that under the current methodology have one mutation and a second IRT that turn out to have CF confirmed.

In January 2020, these findings were discussed with the Fetal, Maternal and Child Health (FMCH) sub-group of the UK National Screening Committee (UK NSC), the body that advises Ministers about all aspects of population screening. Before going further, the FMCH asked that we consult with stakeholders to help inform and assess the impact of these proposed changes and in particular the use of an approach that would avoid reporting carriers, reduce the ambiguity associated with CFSPID and avoid the need for some repeat samples but at the cost of some missed cases.

**Objectives of the project to consult with stakeholders**

In response to these findings and to answer the questions posed by the FMCH the study team wish to:

1. Gather, compare and analyse the views of a range of stakeholders on the proposed CF screening protocol incorporating next generation sequencing (NGS).
2. Use the outcomes to inform discussions and decisions by FMCH group and UK NSC about the proposed protocol
3. Consider what generalisable information on the views of stakeholders on newborn screening could be generated from this exercise to inform other FMCH and UK NSC discussions
4. Evaluate and learn from the exercise to inform future stakeholder engagement activities by the UK NSC and screening programmes.

**Advisory Group**

An informal ‘active advisory group’ has been set up to guide the project. The group is comprised of clinicians, representatives of patient charities, public health specialists, professional bodies and academics. The group has met twice to discuss the stakeholders that should be consulted and the questions they might be asked.

**Literature review**

It was agreed that Lauren Cooper, a manager newly appointed to support the project, should undertake a literature review to determine if experience elsewhere could guide the use of NGS in the context of newborn screening for CF. The results of this are available on request.

**The groups to be reached**

The active advisory group has identified three broad groups of stakeholders that it would be important to engage with. The advisory group has also discussed methods that might be appropriate ways to engage with the different stakeholders, although it remains open to considering other methods.

***Group 1. People with a personal experience of CF, CFSPID or carrier status***

This would include children and adults with CF and CFSPID (Cystic Fibrosis Screen Positive, Inconclusive Diagnosis) and carriers of CF, as well as their parents and wider families. We might also include families who have received false positive results, and people who have opted for carrier testing in the private sector.

We suggest that:

* The views of people in this group are highly important given the significant impact that CF screening will have had on their lives.
* Some sub-sections of this group will be small, e.g. families with CFSPID.
* Most people in this group are unlikely to have expert knowledge of genomics and screening.

Careful planning and expert facilitation would be needed to ensure the topic was discussed appropriately and sensitively. Any engagement activities involving children (under 18s) and people with learning disabilities would require particular thought and, possibly, ethical review.

People in this group could be recruited through charities, CF clinics and social media, with the help of the Advisory Group.

**Group 2.** ***Healthcare and other professionals involved in CF screening and follow-up care and support***

This might include specialist CF doctors and nurses, clinical geneticists and genetic counsellors, screening midwives and GPs, in the UK and abroad. Added to this may be others such as people involved in genomics education and teachers who educate and support children with CF, as well as the CF Trust.

We suggest that:

* People in this group will have some knowledge of genomics and screening and, in some cases, will have expert insight.
* Their views are important, given their clinical knowledge and experience of working with patients and families.
* There are a large number of people in this group.

People in this group can be reached through professional bodies and networks with the help of the Advisory Group.

***Group 3. General public***

We are planning to undertake a more general ‘public consultation’ related to the use of genomic testing when screening for cystic fibrosis as an extension to the current work being undertaken by Sciencewise in collaboration with the UK National Screening Committee and Genomics England to consider the use of whole genome sequencing in newborn screening.

**The questions that we may wish to pose**

Following our last meeting, we identified a number of questions on which we would like to seek stakeholders views, including:

* How is the proposal to use expanded genetic testing in the newborn screening programme for CF viewed by different people and groups?
* What are the anticipated impacts on families and the NHS of avoiding or including the reporting of carriers and CFSPID cases with CF newborn screening?
* How are trade-offs made and valued between ensuring that we do not miss any cases or potentially causing uncertainty or false alarm (ie sensitivity vs specificity) and how is this viewed by different people and groups?

**Further considerations**

Engagement methods and stimulus materials should be accessible and inclusive to enable a wide range of people to take part, including, potentially, children, people whose first language is not English, people with autism, and BAME communities. The project should use robust methods and be clear with participants about the scope for influence.

While we might want different things from different groups, it may be helpful to triangulate opinion from the same or similar groups using more than one methodological approach, and conversely to compare the same method when applied to different people groups.

**Project outputs**

At the outset, we will need to consider what outputs we are aiming for.

The primary audience will be the FMCH group – a group made up largely of clinicians and academics.[[1]](#footnote-1) The project outputs will form part of the evidence that the FMCH will scrutinise in order to formulate advice to the UK NSC on whether next generation sequencing in CF screening should be adopted nationally (objective 2). We hope the findings will also include generalisable information on the views of stakeholders on newborn screening to inform other FMCH and UK NSC discussions (objective 3).

For maximum impact, the outputs should demonstrate that a rigorous process (design, implementation and analysis) has taken place.

We would also like to share the outputs more widely, so that others can use our findings, for example on the UK NSC website and/or as a journal or media article.

**Evaluation**

The fourth objective of this project is to evaluate and learn from the exercise to inform future stakeholder engagement activities by the UK NSC. Plans and resources for evaluation will need to be built in from the beginning, and specialist expertise might be sought for this.

**Timescales**

The broad timeline for the project is suggested to be:

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| April-June 2021 | Finalise project design, hold supplier day and tender for delivery partners. Conduct ethical review if required. |
| June-December 2021 | Field work |
| January - March 2022 | Analysis and reporting |
| April 2022 | Final report available |
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1. For membership of the FMCH see <https://www.gov.uk/government/groups/uk-national-screening-committee-uk-nsc#reference-groups> [↑](#footnote-ref-1)