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Call for views and evidence on non-invasive prenatal testing: response from the PHG Foundation

The UK National Screening Committee (UKNSC) has recommended that NIPT for Down Syndrome, Patau Syndrome and Edwards Syndrome be offered on the NHS to pregnant women whose babies are found to have a high risk of having one of these conditions following the 11-14 week screening tests. The UKNSC has proposed that this should be implemented as part of an evaluation process to understand better how offering NIPT in this way will affect the screening pathway and the choices that women make.

PHG Foundation was the first in the UK to explore the potential of NIPT for use in the UK NHS1 and we have longstanding expertise and interest in this area. We would like to emphasise two key points relevant to many of the consultation questions:

A. We regard the implementation of NIPT for aneuploidy as proposed as a safe and measured approach enabling equitable access to pre-natal testing across England. Subject to approval from the Secretary of State for Health, it will be the first national publicly funded routine NIPT service

worldwide and will provide a significant improvement in the quality and safety of the current aneuploidy testing pathway. We therefore support the introduction of this application of NIPT. However, in order for effective and consistent implementation, it is important that sufficient resources are provided.

B. Our view is that NIPT as applied to aneuploidy screening should be regarded as a novel, but not exceptional, biomarker test. As such, the approach taken by policy makers and regulators should be consistent with other tests, and seek to avoid overemphasising the potential harms associated with the technology. In places, the content and structure of the consultation questionnaire encourages such an exceptionalist approach which could bias responses.

Detailed responses

If this recommendation was implemented fully into NHS antenatal care, what benefits or concerns might this raise for pregnant women and their partners?

Benefits:

- Quicker, easier, safer identification of those at low-risk
- Reduction in the absolute numbers of babies found to be at high risk of Down's syndrome, Patau syndrome or Edwards' syndrome following 11-14 week screening tests, whose pregnancies miscarry as a result of an amniocentesis or CVS which is done to confirm a diagnosis
- Data from evaluation studies including the RAPID study suggest that, for high risk women, NIPT removes a barrier to further testing which invasive testing currently represents. This subgroup of women who undergo testing for information only, can use NIPT for this purpose without putting the pregnancy at risk
- Improved patient satisfaction due to reduction in the decision-making, anxiety and discomfort associated with invasive tests
- Implementation in the NHS will address the current inequity of access to this safer non-invasive test arising from extensive commercial availability
- Increased reproductive choice amongst those women who chose NIPT, receive a positive result and proceed with the pregnancy, using the diagnosis for information only. (Evaluation studies performed as part of the RAPID project2 suggested that 31% of women with a positive test result continued with their pregnancy)

Concerns:

» For those identified at high-risk, a potential delay in having a definitive diagnostic test through amniocentesis or CVS, although the average turnaround time for NIPT in the RAPID study was under 10 days

» Consequent increased distress/trauma if women with positive results opt for termination of pregnancy

» The risk of exacerbating inadequate opportunities for women to give fully informed consent to testing (because of constraints in appointment time; lack of relevant healthcare professional expertise and assumption of patient preferences, etc.)

» Fears that women with a positive NIPT test result might proceed to termination of pregnancy without validation through an amniocentesis or CVS and resultant distress/anxiety in those women

» The literature has raised concerns about routinisation of testing. Unlike the offer of an invasive test, which is carefully considered, there is concern that the ease with which a blood sample test is provided might mean some women enter into the test without sufficient careful thought for the potentialconsequences. Although this concern is equally relevant to existing triple / quadruple blood testing, it emphasises the need for sufficient resources to be made available to support the implementation of NIPT aneuploidy testing

If this recommendation was implemented fully into NHS antenatal care, what might be the implications for the healthcare professionals involved in offering and providing prenatal screening and testing?

Healthcare professionals would need to:

» Develop their knowledge and understanding of NIPT; this will include all midwives (as opposed to just screening midwives) since they will need to discuss NIPT as part of the whole antenatal care pathway

» Improve and maintain their counselling skills despite time pressures, so that NIPT is not regarded simply as another element of blood testing, but is viewed (and offered) as an important test which has significant consequences

» Develop processes to differentiate NIPT from the range of other tests that are offered at this time

The absolute number of invasive tests is expected to fall substantially, which could in turn lead to an overall reduction in skilled practitioners, and invasive testing only being offered in highly specialist centres

Depending on the mode of provision, laboratory and technical staff would also need to be trained and recruited to provide the testing service, including the capacity to collate data from these tests, evaluate their effectiveness and integrate that knowledge into existing and future practice.

If this recommendation was implemented fully into NHS antenatal care, it might lead to an increase in the number of terminations of pregnancies with a diagnosis of Down Syndrome, Patau Syndrome or Edwards Syndrome. What benefits or concerns might this raise?

Benefits:

» More women with pregnancies affected by Patau or Edwards' Syndrome would have the option to avoid the trauma of having a more extended pregnancy and subsequent miscarriage, or a live birth of a disabled child with a severely limited life expectancy

» The increase in diagnoses may include women who previously sought reproductive choice, but found invasive testing unacceptable as a first line test: NIPT may remove this barrier to testing for some women, but it is important to note that not all will necessarily opt for confirmation by diagnostic invasive testing, or for termination of the affected pregnancy

Concerns:

» That women may make decisions without having the opportunity to receive balanced and accurate information about the potential risks and benefits of proceeding with, or ending, a pregnancy affected by any one of these conditions

» If we accept that a valid aim of screening programmes is to improve informed choice, it is difficult to then raise concerns about the collective result of individual choices within a screening programme. However, a wider set of concerns surrounding possible resultant societal issues that might arise from less targeted applications of NIPT have been raised in the literature3, including reduced societal tolerance for disability, 'blaming parents' including increased financial burdens being placed on them coupled with a reduction in the provision of services for children with these conditions, and legal, moral, social and psychological issues around termination of pregnancy

Do you think the UK National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme are appropriate for appraising prenatal screening programmes?

We consider this question to be somewhat irrelevant in the context of NIPT since the suggestion is that NIPT is one of the technologies used in the process of diagnosing affected pregnancies (an assay) and is not a screening test itself and so does not have to fulfil the criteria. These comments thus relate to the appropriateness of current NSC criteria for appraising prenatal screening programmes in general rather than the use of NIPT which will supplement the existing aneuploidy testing pathway following a positive 11-14 week screening test. Nevertheless, they would also become relevant if non-invasive technologies were to be used in the future as the primary prenatal screening modality.

The PHGF has some general concerns about the current criteria used in the UK by the NSC. In the PHG Foundation document Genetic Screening Programmes: An International Review of Assessment Criteria we undertook a literature review of genetic screening appraisal as part of a wider NSC review of screening policy (published 2014). We identified that genetic screening often does not fit well with the overall criteria used to appraise a wide range of screening programmes e.g. those for common chronic diseases, which are concerned with reducing morbidity and mortality in the population.

The scope and purpose of prenatal screening programmes are concerned with offering reproductive choice whereas the first group of NSC criteria relate to reduction in population morbidity or mortality for an 'important health problem' (criterion 1). Use in prenatal screening presupposes that it is important to be able to offer all pregnant women the opportunity to avoid the birth of a baby who is likely to die or be severely affected by disease that is identifiable before birth. Women would have the choice to terminate the pregnancy. Use of the screening criteria for decision making in prenatal testing implies that any screening programme must satisfy the primary criteria that the availability of this choice, (rather than the condition itself) is an important health issue. The psychological, physical and social effects on the mother/parents throughout pregnancy and in raising the child are thus the outcomes of concern.

The use of NIPT as either the initial screening test (not yet proposed) or as part of the follow up diagnostic testing following a positive screening test must then 'pass' the further criteria related to the availability of a suitable screening test and definitive follow up diagnostic testing, the effectiveness and overall configuration of interventions offered and available for individuals discovered through the screening, and the overall effectiveness, cost effectiveness, practicality and public and professional acceptability of the programme as a whole.

We have set out above (in responses to questions 1 and 2) the potential benefits and harms of using NIPT as a modality for either initial screening or follow up diagnostic testing which broadly relate to the NSC criteria:

» The test is simple, safe, precise and validated (criterion 5)

» It may enhance the ability to accurately determine risk (criterion 13)

» Is clinically, socially and ethically acceptable to health professionals and the public (criterion 14)

» Increases benefits and reduces harm (criterion 15)

» As regards opportunity cost (criterion 16) it is more difficult to assess prenatal screening programmes (whether or not using NIPT) because of the difficulty of valuing reproductive choice. Whilst we may argue that NIPT renders the programme more cost effective than other testing modalities, there are no absolute cost effectiveness measures of the value of reproductive choice. As argued by Stephen John3, the inclusion of the extra costs to society and individuals of raising a very sick or disabled child is generally considered to be unacceptable in decision-making over prenatal screening programmes

Information and counselling

How would you rate the information and counselling currently provided by the NHS to pregnant women and their partners to help them make decisions about currently available prenatal screening (e.g. using ultrasound) for genetic conditions during pregnancy, if you have experience or evidence relating to this?

Anecdotal evidence suggests that provision of information and counselling is very variable depending on region.

How would you rate information and/or counselling provided by the NHS about NIPT available as part of research studies or through the private sector, if you have experience or evidence relating to this?

It is difficult to assess the access to general information on NIPT for patients outside formal research studies or outside areas where an NHS service has been established, but several reviews in the literature highlight the importance of careful non-directive pre- and post-test counselling to avoid undermining informed consent and mitigate against increasing routinisation. The RAPID implementation study group developed materials and provided training sessions for healthcare professionals offering NIPT. The study group also produced materials for parents, which were validated by parent groups and healthcare professionals. Evaluation of parent experiences showed that 88% were found to have made an informed decision, and feedback on the resources was very positive. The

study highlighted the critical importance of providing adequate resources in an implementation setting in the NHS to train healthcare professionals to deliver pre- and post-test counselling, and to ensure sufficient time to discuss NIPT and its implications with parents. Robust efforts need to be made to provide these resources in what is already an overstretched service.

How would you rate the information and/or counselling currently provided by private healthcare clinics to pregnant women and their partners to help them make decisions about NIPT, if you have experience or evidence relating to this?

A systematic review by Skirton et al.5 has identified a number of companies who do not provide adequate information as recommended in professional guidelines, for example, to advise of the need for confirmatory invasive testing in the case of positive results, and the inability of any test to guarantee the health of the baby.

Anecdotal evidence suggests that women are seeking confirmatory invasive testing in the NHS, and in some instances express concern and anxiety regarding the meaning of results from private providers.

What information about NIPT and the conditions being tested for do you think should be conveyed to pregnant women and their partners? How do you think that information could best be conveyed and by whom?

That NIPT is safe, convenient and highly accurate when used for the aneuploidy screening but it is not a definitive diagnostic test. It should be regarded as a guide as to whether to consider further invasive testing.

NIPT does not rule out other genetic abnormalities beyond those that are specifically tested for.

That its use within the NHS is limited to medical purposes (and not social ones such as sex selection as this is illegal).

That irrespective of whether clinics are 'one-stop' (offering serum screening, ultrasound scan and risk result on the same day) or 'two-stop' (which offer ultrasound scan and blood draw for serum screening on one day and risk result returned at a subsequent date), women should be provided with adequate counselling and have sufficient time for reflection. Midwives are in general best placed to offer this information rather than GPs (who typically do not have the requisite training).

The onus (from an ethical and practical point of view) is on providing the pregnant woman with information to enable her to make an informed decision.

What might be the implications for the NHS of increasing numbers of pregnant women purchasing NIPT through the private sector?

That women purchasing NIPT through the private sector, as in the NHS, might not be counselled to a consistently high standard; and consequently that they might not understand the potentially benefits and risks of proceeding with the test.

That purchasing NIPT through the private sector could result in growing inequity of access.

That more women might seek NIPT privately and then, in the event of a positive test, wish to be referred for invasive testing by amniocentesis and CVS accessed via the NHS.

That there might be a lack of capacity within the NHS to meet the demand for invasive testing, and subsequent management for these women.

What benefits and concerns might be raised if pregnant women were able to purchase NIPT directly from providers (e.g. where a kit is sent to the pregnant woman in the post), rather than through a healthcare clinic following a face-to-face consultation?

Benefits:

» That NIPT testing would be more accessible to a wider range of women who perhaps could not attend a healthcare clinic. This might include women who lived a long way from a clinic, or those who were fearful of stigmatisation (either from their own families or the wider community); this might include very young women (including children below 16). Provision of these technologies on a direct-to-consumer basis would help to ensure that women had equitable access to these technologies, an important principle which should underpin the provision of publicly funded health services

Concerns:

» That it might be more difficult to ensure that blood samples are of a high enough standard for accurate, consistent testing results

» More likelihood of sample mix-up or contamination than where samples are collected by health care providers

» Women might be less likely to be fully informed about the testWomen might be more likely to be pursuing the test for their own reasons (such as social sex-selection)

» Depending on the methods for feeding back results, this could lead to concerns that women undergoing testing have a lack of understanding about the significance of the information provided by testing

A small proportion of NIPT tests will return an inconclusive result, even if repeated. How should healthcare professionals, both in the NHS and in private clinics, deal with inconclusive results?

The consent process should address the potential for inconclusive testing and depending on the frequency of incomplete tests within a representative patient population, the impact of such testing

Given the potential for anxiety arising from inconclusive results, there should be clear protocols on offering repeat NIPT or invasive testing, and ongoing efforts to improve knowledge regarding the reasons for inconclusive results as understanding of the assay develops

What issues are raised by incidental findings that can arise following NIPT (such as genetic abnormalities or cancerous cells in the pregnant woman), both in the NHS and in private clinics?

NIPT is an assay not a test. If the purpose and scope of testing (purpose, patient population and reliability) is clearly defined, as in this proposed application, the probability of incidental findings arising is low because of the analytical approach being adopted. However, if NIPT is to be used more widely, the consent process should include a discussion of any additional or incidental findings that might be generated by the test; their frequency; the extent to which they might be reported and any additional actions or management that might be suggested or required if they are detected.

There should be clear consensus-based protocols to ensure a consistent approach to reporting incidental findings, and if deemed appropriate, mechanisms to minimise undesirable incidental findings.

There have been case reports of NIPD revealing cancer in the pregnant woman (in the case of a chimera). Depending on the likelihood of this occurring, this possibility might need to be included as part of the consent discussion.

The range of issues that need to be discussed by the healthcare professional or the person involved in the consent process, suggests that this should be done by a designated professional, who has been trained to a high standard. Knowledge of NIPT by midwives or GPs should not be assumed.

What should NIPT be testing for?

In the future, NIPT may allow pregnant women and their partners to test their unborn babies for a wider range of genetic conditions, including those that develop in adulthood. It may also be possible to find out about non-medical information relating to the behaviour and physical appearance of the future child. It is possible to use NIPT for 'whole genome

sequencing', which reveals the complete DNA make-up of the unborn baby. At the moment this is very difficult and expensive, but it may become cheaper and easier in future.

Should potential parents be able to find out the sex of their unborn baby for non-medical reasons from 10 weeks of pregnancy using NIPT? Please give reasons for your answer.

The sex of the baby may be communicated to parents at the hospital's discretion during the mid-pregnancy ultrasound scan (between 18-20 weeks gestation). Informing parents about the sex of their baby substantially earlier in the pregnancy might enable more parents to access termination of pregnancy if the child is of the 'wrong' sex, on the basis that they do not wish to continue the pregnancy on psychological grounds.

Is there more likelihood of women (especially from some cultures) being forced into early testing and termination of pregnancy? How can women be protected against these pressures?

Alternatively should parents be trusted to have this information at the time it is generated and reported? To withhold information seems paternalistic and inconsistent with a health service which encourages users and consumers to take more responsibility for their health.

What genetic information, if any, do you think parents should be allowed to find out about their unborn baby using NIPT? Please give reasons for your answer.

Serious or life-threatening conditions that have their onset during pregnancy or very early life that are medically actionable.

Serious or life-threatening childhood onset conditions regardless of whether they are actionable or not. For informational purposes, parents may wish to know about conditions that their children may develop during childhood even if these are not treatable e.g. muscular dystrophy.

Within the ethical delineations described above, consideration of widening the application of NIPT may involve conditions which do not fulfil the national screening criteria (as we have described the incompatibility of the criteria previously), but rather reflect the primary aim of the programme to provide information and allow parents to exercise reproductive choice.

In addition to these ethical considerations, any expansion in this area must look very critically at the sensitivity and specificity of any assay used to provide this information.

What genetic information, if any, do you think parents should not be allowed to find out about their unborn baby using NIPT? Please give reasons for your answer.

Serious adult onset conditions that are medically actionable.

Serious adult onset conditions that are not currently medically actionable (on the basis that by the time the child has developed symptoms, there may be a treatment or cure for those conditions).

That the majority of genetic information should not be communicated. This would be on the basis that we are at a very early stage of understanding about the significance of genetic information and the extent to which this is predictive of future disease. Thus our knowledge is very preliminary: we need to understand far more about the penetrance of disease; the extent to which different types of risk factors combine; and the incidence of diseases (even in diseases like breast cancer caused by the BRCA1 and 2 variants, which have been well-described, we have limited understanding of this disease in families without a family history of disease).

In the past, two elements have informed policy making in this area: the first set of concerns address what is in the best interests of the child. These principles have informed decisions that are made about testing and treatment of children once they are born. But in connection with pre-natal testing, policy makers in the UK also take into account wider societal issues. So a concern that might arise from allowing parents extensive information about their unborn child's genetic information is that if this were adopted widely through society, that these attitudes could be regarded as eugenic. This could lead to a world where people were less tolerant of people who were not 'normal' and could lead to a negative feedback loop whereby less support is made available for disabled children; there is more discrimination and stigmatisation. In short – the fear is that the world would move closer to a dystopian future, where any form of 'abnormality' was regarded as socially unacceptable.

Do you think whole genome sequencing of unborn babies using NIPT should be allowed? Please give reasons for your answer.

The PHGF opposes offering whole genome sequencing of the entire fetal genome of unborn babies using NIPT on a universal basis. It is premature to offer such testing within routine clinical care or public health screening, on the basis that there is not sufficient understanding of what the results of WGS testing means to be able to interpret results reliably, and understand the clinical meaning of the results for the unborn child and their family. In particular, the penetrance of many genetic diseases is not sufficiently understood.

If combined WGS/NIPT testing were used in this way the provision of WGS in unborn babies might result in increased numbers of terminations of pregnancy or could result in overdiagnosis and medicalisation.

However, it is possible that targeted WGS of unborn babies using NIPT as a 'virtual panel test' could feasibly be used as a replacement technology to detect genomic aberrations that are already tested for or where tests are currently in development. Using combined WGS and NIPT in this way would require sufficient technical equivalence, sensitivity and specificity to be achieved.

All providers must be clear about the scope of testing that is offered, the results that might be generated and possible outcomes.

If population wide NIPT is implemented for aneuploidy screening, it is vital that anonymous test results are able to be linked to a national register of pre-natal, birth and extended post-natal follow-up. A comprehensive programme of data collection, registration and evaluation of all pregnancies analysed by NIPT is needed in order to construct the evidence base on which future WGS-based prenatal testing could accurately be provided.

Implications for wider society

What, if anything, might the increasing availability and use of NIPT mean for people living with genetic conditions? Please provide evidence or examples if possible.

As mentioned above, there are fears that the increasingly availability and use of NIPT might result in greater stigmatisation and discrimination against individuals and families with genetic conditions, and in the longer term, a disproportionate reduction in services available to support those children and families. A reduction in the number of people with the specific genetic conditions testing for via NIPT should not result in any necessary support services for those affected being cut.

There is also a fear that families who chose to proceed with a pregnancy knowing that they will have, or are at risk of having a child affected with a genetic condition, will be regarded as 'irresponsible'. This could result in the increased financial burden on these families for care of children being regarded as legitimate and their responsibility, and hence not eligible for wider state support.

As these technologies become more accessible, it is likely that there will need to be renewed analysis of what the social contract means (between citizens and the state) as well as a review of other forms of support such as insurance, so that in the future, there remains a sense of social solidarity rather than genetic determinism.

Regulation

Is current regulation covering the provision and marketing of NIPT in the UK sufficient and appropriate?

There needs to be more rigorous regulation of NIPT particularly tests that are marketed and provided on a direct-to-consumer basis. This includes:

» Policing the validity of the claims that are made about the nature of the test, the efficacy and likely outcomes (advertising standards)

» Ensuring the validity of scientific and analytic validity

» Ensuring that clinical claims are backed up by appropriate evidence of performance evaluation studies

» Clarifying the pathways for NIPT tests to be developed (with input from statutory agencies such as the MHRA)

» Considering the impact that Brexit will have on the implementation of the new EU IVD Regulation in the UK (and considering feasible alternative approaches)

Ethical values

What ethical values do you think are important or relevant in the context of NIPT?

All the values identified above are relevant and we have alluded to each of these in answer to other questions within the consultation.