Implementation of the ‘genomic’ sample at diagnostic biopsy to optimise molecular testing:

Introduction through the 100,000 Genomes Project into clinical practice and research within the NHS

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# Background

Advances in molecular technologies are driving the evolution of precision medicine, and molecular tests are increasingly part of cancer diagnosis. As more ‘clinical actions’ and treatments are defined by molecular biomarkers, diagnosis will become an integration of histological and molecular analysis. In addition to diagnosis, monitoring will be undertaken by molecularly profiling on multiple occasions during the cancer journey: via sampling of the tumour at primary or secondary sites and/or using circulating cell free tumour DNA as a liquid biopsy of the tumour. Molecular profiling currently comprises analysis of the DNA for small mutations, copy number variants and/or fusion genes; in due course signatures of expression of the RNA, proteomics and metabolomics may also be routinely employed as biomarkers combined with morphological informative to inform on cancer behaviour and direct treatment.

As well building a tissue collection for the programme itself, the roll-out of the 100,000 Genomes Project (100KGP) offers a significant opportunity to effect elements of NHS transformation which will accelerate the delivery of personalised medicine for cancer. Inclusion of biopsy samples in the programme ensures that those patients with the most aggressive disease benefit from the advances in molecular medicine, and helps realise the full potential of this programme, and more broadly molecular diagnostics. Furthermore, embedding this genomic analysis much earlier in the diagnostic process should enhance the effectiveness of existing interventions while building the infrastructure to allow the realisation of further benefits in this area to be implemented in a low cost manner. Importantly, this also allows access to those individuals with the worst prognosis disease, who arguably, could benefit most from this advance in diagnosis and care.

In terms of whole genome sequencing, the analysis of biopsy samples, which will come from the most clinically challenging scenarios, will place the 100KGP and NHSE at the international forefront of molecular medicine.

# Molecular pathology using biopsy samples: the clinical need

The majority of tumour genome data generated to date has used samples obtained from tumour resection at the time of surgery, because this is when samples of sufficient size are readily obtainable. Whilst there are challenges around the use of biopsy material for WGS, there are a number of situations where the genomic analysis of diagnostic biopsies offers significant clinical and research advantage:

## Analysis of chemonaive tissue

Analysis of chemonaive tissue diagnosis from patients to whom neoadjuvant chemotherapy (NACT) is routinely administered. Patients undergoing NACT generally reflect those with the most aggressive and clinically challenging form of the disease, for whom WGS has the potential to identify genomic alterations possibly not seen in earlier stage disease that could offer new therapeutic opportunities. Chemotherapy causes mutations within tumour DNA, so a tumour genome sequence after chemotherapy is harder to interpret than a pre-treatment tumour genome sequence. In many cases, it is these patients that represent a significant unmet clinical need and so are particularly relevant to the 100KGP where characterisation of the tumour genomic landscape could direct therapy, going forward.

* **Breast cancer:**  approximately half of all patients with the aggressive Triple Negative phenotype, and many larger cancers of any subtype, will receive NACT, and NACT is standard of care for patients presenting with inflammatory breast cancer, and for locally advanced breast cancer.
* **Ovarian cancer:** >65% of women are diagnosed with ultrasound-guided biopsy and go on to receive NACT

## Inclusion of patients who would not typically proceed to resection:

* **Lung cancer:** The National Lung cancer audit received data on 34,468 patients diagnosed with lung cancer in 2013, representing 98% of the predicted UK incidence [1]. Only 15.1% of these patients will receive an operation. Patients with stage IIIB-IV NSCLC will be predominately diagnosed with a percutaneous or endoscopic biopsy and do not undergo surgical resection but are treated with systemic therapy either in the metastatic setting or as part of a radical chemo radiotherapy regime. Furthermore, patients with Small Cell Lung Cancer rarely undergo surgical excision but are treated with chemotherapy and radiotherapy.
* **Prostate cancer:** There are several scenarios whereby patients diagnosed with prostate caner do not undergo surgery:
  + Patients undergoing active surveillance
  + Patient unfit for surgery undergo ‘watchful waiting’
  + Patient undergoing an alternative radical therapy eg radiotherapy, brachytherapy, HIFU
* **Metastatic disease:**
* Patients presenting *de novo* or on relapse with metastatic disease are unlikely to undergo surgical management and provide a therapeutic challenge that may significantly benefit from WGS.
* **Renal Cell Carcinoma:**
* Not all patients with metastatic RCC will undergo nephrectomy (particularly those with ‘bad’ disease biology). Moreover, relatively few patients will undergo metastasectomy for advanced disease so biopsy of metastatic sites is necessary to study and characterise advanced disease, particularly in relationship to the primary.

These all represent significant clinical challenges, and without the opportunity to include biopsy samples in the 100,000 Genome Project would be lost to the study.

# Opportunities afforded by inclusion of biopsy samples in 100KGP

If we can advance structures within the programme to include and successfully sequence tissue from biopsies in these types of contexts, this offers very clear advantages.

**Transformation of clinical practice.**As detailed above, as stratified cancer care improves and advances, integrated morphological and molecular characterisation of tumours will be required at first diagnosis, so as to administer stratified/targeted therapies as immediate/neoadjuvant treatment. Molecular characterisation will then serially be undertaken throughout the cancer journey, each time the tumour is sampled (often by needle biopsy). Even if ultimately routine genomic analysis will be in the form of targeted panels, the need to apply to biopsy samples remains. Therefore, it is essential to advance biopsy tissue collection of a quality and quantity appropriate for molecular profiling as routine, in parallel with developing technology for application to limited biopsy material.

**Addressing a significant unmet clinical need through analysis of some of the most aggressive tumour types.** Radiotherapy, with or without concurrent or sequential chemotherapy is given in the radical setting with curative intent to approximately 8.4% of the UK lung cancer population [2], many more will receive palliative radiation. The potential for next generation sequencing to identify drug targets for novel drug and radiation combinations is an understudied area with significant therapeutic and commercial opportunity. Similarly, disease presenting at advanced stage and identifying the genomic evolution of a tumour across time will open new therapeutic avenues.

**Dramatic expansion of numbers**of patients that can be included in 100,000 Genomes Project.

Given the number of patients that require NACT or warrant active surveillance, without the inclusion of biopsy samples there will be significant loss of the cancer population to the 100KGP. Small cell lung cancer patients very rarely undergo surgical resection. Diagnosis is made using biopsy specimens. Although tumours respond initially to cytotoxic chemotherapy and radiotherapy, relapse rates are high and further lines of effective systemic therapy are an unmet clinical need. Without the inclusion of biopsy samples in the 100,000 genomes project the small cell lung cancer cohort will be virtually non-existent. In breast cancer, approximately half of patients with Triple Negative disease and almost all patients with Inflammatory Breast Cancer will undergo neoadjuvant chemotherapy, again severely limiting their representation in the study.

The inclusion of biopsy samples not only will make the 100KGP unique in terms of data from previously unexplored spectra of disease, but also provides equity of care to those individuals with the most advanced or challenging disease.

**Opportunity to undertake novel research**via inclusion of tumours and patient groups not typically undergoing surgical resection, whose management is frequently challenging, and from whom few whole genome analyses have been undertaken to date. For example, the two landmark next generation sequencing papers by The Cancer Genome Atlas on lung adenocarcinoma and lung squamous carcinoma reported whole exome sequencing data for only 56 and 41 stage III-IV patients, respectively and only in 11 patients with stage IV disease in total [3,4].

Stage IV patients are the main stage group of patients who receive cytotoxic chemotherapy or targeted drug therapy and are therefore of particular interest to academic groups, the biotechnology and the pharmaceutical industry with respect to novel drug target discovery. There is very little data on how well genetic analysis of early stage disease reflects later stages, highlighted by studies showing both concordance and discordance of key driver mutations between primary and metastatic pairs [5-7]. Whole genome analysis of late stage disease would also help identify novel copy number changes or translocations that may be amenable for systemic therapy.

**Achieving this transformation in clinical practice will require adaptations to each step of the cancer diagnostic pathway, as described below.**

# Integrating genomic analysis into the clinical pathway

## Acquisition of extra biopsy material

Typical practice to date has been to minimise the amount of tissue taken at biopsy with the focus on ensuring enough material for a definitive diagnosis. Furthermore, biopsy samples are frequently largely depleted by routine diagnostic histopathology. Currently, utilising the tissue remaining after routine diagnostic biopsy, for the SMP2 Matrix study, insufficient DNA is obtained to undertake a targeted panel (50ng) in >40% of biopsied lung cancers (personal communication, David Gonzalez de Castro). Thus, additional biopsy samples, or introduction of novel sample handling techniques, are required to routinely undertake successful molecular pathology investigations on cancer patients, in particular if this is to be whole genome sequencing.

Biopsy samples for genomic analysis could be acquired either at the time of initial diagnostic investigation or as a separate second procedure. Both clinicians and patient advocates (see below) favour the practice of additional biopsies at the time of diagnosis, being less invasive and not requiring a separate clinic appointment. Furthermore, this has the advantage of integrating genomic analysis into routine care and allows parallel morphological and genomic analysis in space and time.

## Risk/Benefit assessment of additional biopsies

**It is standard practice for clinicians (radiologists, gastroenterologists, respiratory physicians) to take multiple biopsies in order to provide sufficient material for definitive diagnosis. Here, we address the potential risk involved in taking additional biopsies for genomic analysis.**

**Breast core biopsy** is a safe procedure with very low complication rates.  The main complication is ‘significant’ haematoma, which is reported to be ‘less than 1%’.  This complication is more frequent with vacuum biopsy (4%), but is not increased even in women on anticoagulant treatment [8]. Taking 2-4 biopsies per lesion is not associated with any additional complications and pain is not an issue if sufficient local anaesthetic is administered.  Pneumothorax is very rare and is not referred to in the consent as the risk is much less than 1 in 10,000 (Robin Wilson, personal communication).

For **ovarian cancer,** the BritROC trial is a good example both of the acceptability of additional biopsy and the low risk associated with this practice. Less than 2% serious adverse events were reported in BriTROC trial, predominantly hospital admission for observation of possible bleeding (James Brenton, personal communication). It is also worthwhile noting that these are biopsies in relapsed disease which are technically more challenging, so risk in primary disease would likely have lower complication rates.

In the **lung,** percutaneous lung biopsies are performed under CT guidance and with sedation for peripheral lung tumours. These are general performed using a 18-21G needle, a co-axial technique allowing multiple passes of the needles with only one lung puncture is part of the British Thoracic Society guidance [9]. The main risk of lung biopsy, haemorrhage and pneumothorax are not increased with multiple passes of the needle [9]. Bronchoscopy is used for primary diagnosis of endobronchial lesion and is performed under sedation. Forceps are used to take pieces of tumour tissue for diagnostic use. There is no evidence to suggest any correlation of complication risk and number of pieces of tissue taken for analysis [9]. Endoscopic ultrasound and transbronchial needle aspiration (EBUS-TBNA) is now routine practice in most centres and is a safe and highly accurate way of collecting tissue for diagnosis of NSCLC or SCLC either from the primary tumour or mediastinal lymph nodes. There is no evidence to suggest any correlation of complication risk and number of pieces of tissue taken for analysis. Collecting a sample for genomic analysis, from additional passes would extend the procedure and duration of sedation, by a matter of a few minutes (<5 minutes).

In **Renal cell carcinoma,** several clinical trials (PREDICT and TraceRx RCC) involve multiregion biopsies of primary and metastatic sites with 16G needles, which in general provide sufficient DNA yield for exome sequencing generally 1-2 micrograms of DNA per good quality biopsy. This is done by carrying out 1 puncture followed by insertion of a coaxial, from which multiple tumour/metastatic regions are sampled. In 3 years and around 1000 procedures no significant (requiring blood transfusion) bleeding complications have occurred (James Larkin, personal communication).

In **prostate cancer,** multiple biopsies are routinely taken at diagnosis. The taking of additional biopsies for research does not incur significant complications (Johann de Bono, personal communication). When using a transperineal targeted approach, the safety profile is very high. Rates of infection or sepsis (approximately 3 per 1000 procedures) are so low as to make demonstration of incremental risk from additional cores difficult. Case series have shown that groups having additional core biopsies taken (for example in the NCRN Progeny Trial) have similar risks in terms of haematuria, haematospermia and pain post-biopsy, compared to those who do not have additional biopsies. Approximately 50% of men approached for additional biopsies as part of the NCRN Progeny Trial gave their consent (Mark Linch, personal communication).

For **gastrointestinal biopsies**, there is a very small risk of a major bleed from endoscopic biopsy, with most units quoting a figure of approximately 1 in 1500 cases [10]. Major bleed risk is not increased even if the patient is on NSAIDs, and BSG guidelines also quote minimal increased risk of diagnostic biopsy in thrombocytopenia and anticoagulation [11]. The majority of diagnostic endoscopy cases will have endoscopic biopsies taken for clinical reasons and there is little evidence to suggest that adding in extra biopsies for research increases this risk. This is highlighted in an SOP from Boston childrens hospital (attached), where they quote minimal risk from taking up to 6 research biopsies in each colonic region from children, which is way in excess of what is proposed here.

**Thus, there are strong data indicating that acquisition of additional biopsy material at the time of initial diagnostic biopsy is associated with minimal additional morbidity or operator time, even in more invasive contexts such as bronchoscopy or colonoscopy, and as such this is likely to be an acceptable change in practice.**

## Approaches to consenting

**Taking detailed consent at time of diagnostic biopsy for a genomic study of cancer is logistically inappropriate, as the majority of biopsied patients will transpire to have benign disease. It also raises ethical questions regarding how such consent should be taken and what its focus should be. Hence, an approach is required that defers the consent for 100KGP until after the diagnosis of cancer has been made through the routine histopathology sample.**

### Transformation to routine acquisition of molecular-ready biopsy material as standard clinical practice

As molecular genetic analyses become standard of care for cancer diagnosis, routinely taking extra material for genomic analyses at first diagnostic biopsy for possible cancer is likely to become normal clinical practice, and thus covered by the routine biopsy consent. Thus the sample would be routinely processed within NHSE diagnostics (down the molecular-friendly pathway) and stored within the diagnostic tissue archive. It would then be accessed for molecular studies as appropriate to the histological diagnosis. Modification of tissue handling may be required, to facilitate WGS, but this should ensure the tissue is still amenable to histological assessment. It may be that the ‘genomic biopsy’ will be required to secure a histological diagnosis, it may be used for genomic analysis or it may not be required. In some situations, assessment of all biopsies is likely to be essential, for example, with prostate biopsies. There are analogous situations in which additional samples for specific tests are taken: in routine germline genetic diagnostics, blood is taken in Lithium heparin tube for a chromosome-based analysis and at the same time take a sample in an EDTA tube for DNA extraction. The extracted DNA may never be used, may subsequently be used for clinical diagnostics, or indeed (following appropriate consent) be used for other studies.

**Such change in practice would require support from key clinical stake-holder groups. These include those who take the biopsies (interventional radiologists, surgeons and oncologists) and those under whose responsibilities the samples are processed (pathologists).**

### Options to address consent requirements in interim transition period

#### Option 1: Development of bespoke Genomics England pre-consent form

In the meantime,in the transition period, to expedite adoption of this process locally and thus facilitate transition, an interim strategy would be to adoption of a brief consent form by which the patient ‘pre-consents’, ie the patient consents to storage of extra biopsy material for ‘potential future genomic studies’, recognising that specific consent will later be taken for the specified genomic study in the event that the patient is eligible following review of the diagnostic biopsy. This model of a brief ‘pre-consent’ form is already routinely used by some trusts and has been deployed across trusts ahead of specific research studies (eg the POETIC breast cancer study). Limitations of this model include:

* Requirement to store samples in HTA-compliant facilities and destroy samples in HTA-compliant fashion
* If pre-consent were developed through Genomics England protocol and research ethics, it would be linked to and require mention of the 100,000 Genomes Project
* The sample would be a ‘research’ biopsy, thus raising issues around how costs of acquisition, processing and storage would be met
* Even with the simplified pre-consent form, there is significant time involved in the consent process, which has particular impact in those settings where currently only verbal consent is required for biopsy, such as in the majority of breast patients.

If a ‘Genomics England biopsy consent form’ approach is used, then any samples consented by this means would come under the responsibility of Genomics England; this would include a significant proportion of patient samples ultimately ineligible for the 100KGP.

#### Option 2 Use of local tissue banking consent processes (where available)

A pragmatic approach at this stage, along the ‘pre-consent’ model, would be to make use of existing local Tissue Bank biopsy consent forms, providing generic consent for use of biopsy material for research. If, post-diagnosis, the patient is considered eligible for the 100KGP, the patient would then be approached for specific consent to the 100KGP, and the research biopsy released to the project (with associated data). At the time of consent to 100KGP, blood samples for germline DNA and ‘omic studies would be collected, thus all samples will be pre-treatment, fulfilling the requirements of the project.

## Adaptation of sample handling processes

As molecular pathology evolves, the routine integration of genomic analysis with morphological assessment implies changes in sample handling. Thus, additional biopsy material for genomic analysis may not need to be examined histologically for diagnostic purposes. Clearly, if the ‘diagnostic’ biopsy does not provide a definitive diagnosis then the ‘genomic’ biopsy would need to be reviewed. However, where a malignant diagnosis is made on the diagnostic biopsy, the genomic biopsy can then be re-accessed if the patient is deemed eligible for molecular studies. The “molecular study” may include the 100,000 Genomes Project, the Stratified Medicine Programme (SMP), other research, or (for some tissues now, and in due course for many more) routine molecular diagnostic tests.

Tissue samples for histopathological analysis are fixed using formalin, which offers superior morphology but damages the DNA, introducing artefactual mutations and preventing high quality genome sequencing. With current molecular technologies, changes are therefore needed in the sample handling process to ensure that ‘genomic’ biopsy handling is optimised for genetic analysis. This may require use of new nucleic-acid friendly fixatives such as PAXgene and UMFix, shorter fixation times in standard fixative such as NBF, or indeed processing fresh followed by freezing. These approaches have the advantage of maintaining the tissue in a condition that allows for histopathological analysis, so facilitating the transfer of the ‘genomic biopsy’ to diagnostic material, should the initial diagnostic biopsies be insufficient. Alternative fixatives are significantly more expensive than formalin, but only small quantities would be required for biopsies (these alternative fixatives could not be applied to large specimens), and over time, technologies are likely to evolve which may make routinely fixed tissue more usable. Furthermore, InnovateUK are keen to support development of innovative technologies facilitating safe, easy ‘snap-freezing at the bedside’ for biopsy samples. Formal assessment of these alternative methods of sample handling is being undertaken as part of the Experimental Phase II Plan.

## Evolving sequencing protocols

The Genomics England sequencing working group is working with Illumina to develop protocols which will further reduce DNA input for industrial throughput sequencing. By decreasing the quantity of input DNA required for sequencing in addition to taking extra biopsy material and storing it appropriately, genome sequencing using biopsy material can be realised at large scale as a means to achieving stratified medicine within the NHS.

# Ethical considerations

The taking of multiple biopsies at diagnosis is routine practice, though usually this material is all submitted for histopathological review. Some centres have generated generic consent forms for additional biopsies to be stored for future research, however, in some instances ethics approval has been revoked since it was deemed that such consent covered only excess diagnostic material. Taking biopsies specifically for a research project at a separate time, following diagnosis, is ethically acceptable, but requires additional clinic appointments and is inconvenient for patients. This approach also does not facilitate the incorporation of genomics into standard patient care.

It is routine to take 2-3 core samples for diagnosis. If one of these is set aside for genomic studies but not used for diagnosis initially, as suggested above, then it is surplus and can then be used for research legitimately as it is not an extra sample per se.  If the other cores are not diagnostic then this 2nd or third sample can be analysed in the usual way.  Potential problems arise when the sample is placed in a different solution, such as RNA-later, which is then not compatible with normal histological assessment (this then becomes an additional sample as it can only be used for research purposes). The use of histology-compatible fixatives would overcome this.

These considerations are important in the practicalities of integrating genomic biopsies into routine practice. It is absolutely appropriate that patients undergo full, informed consent for inclusion in studies such as 100KGP, but as genomic testing becomes routine, then this becomes part of the diagnostic process.

# Patient Advocate Response

In gathering evidence for this paper, a number of patient advocates have been consulted, selected to represent the cancer types of relevance to the 100KGP, and also for experience in specific areas, for example being involved as advocates taking consent for tissue banking.

Advocates were asked their view on acceptability of additional biopsies for research, and for additional biopsies taken at the time of diagnosis compared to research biopsies taken as a second procedure. They were also asked to comment on the pre-consent process outlined above, and on the draft pre-consent form.

The responses are both informed and informative. Overwhelmingly, **advocates felt being involved in research was a positive and important component to patient care. It was felt that molecular pathology was an important development and that patients wanted to be part of this**. However, it was highlighted that patients and the public have a fear of ‘genetic research’, so attention to wording in the consent process is important, and the benefits of genomic research should be explained.

Similarly, all advocates felt taking additional biopsies at the time of diagnosis was preferable to a second procedure, in terms of patient discomfort, risk and convenience. Also, it was agreed that the pre-consent process was preferable to full consent to something as complex as the 100KGP at this point in the clinical pathway. However, it was pointed out that there is a need to consider the time required for patients to make decisions, particularly if this is done at the stage of first cancer diagnosis (which should be considered in resource implications, see below).

There was general approval of the pre-consent form, although a number of advocates felt it should be more generic and one suggested that the emphasis on the 100KGP to the exclusion of other research, or research in general, could give the impression that this was in fact a consent process for 100KGP. It was suggested that a more general ‘consent to research’ might be preferable, with the second stage consent being specific. Following these discussions, a decision was made by Genomics England to adopt the more generic local Tissue Bank consent forms, until such time as consensus is reached to adopt processing of genomic-friendly biopsies as standard of care. A key advantage of this approach is that more detailed discussion around genetic research is deferred to a stage when there is more time for the patient to make informed decisions, a point raised by advocates during this consultation.

# Resource implications

The taking of additional biopsies, different sampling handling and the requirement for consent all have resource implications, though this will vary according to tumour site, since the clinical support needs differ. It seems preferable for the more complex procedures (lung, ovarian, prostate) that, at least initially, additional biopsies will be confined to units with appropriate support and expertise. The TRACERx consortium includes only centres that perform repeat tumour sampling in the metastatic setting as part of routine clinical practice for some patients. These centres have appropriate interventional radiology suites to perform biopsy procedures, experienced thoracic physicians highly competent in endobronchial ultrasound-guided (EBUS) tumour sampling and interventional radiologists competent in imaging-directed tumour sampling procedures. In the case of ovarian cancer patients, resource implications for abdominal biopsies are 6hr observation with nursing obs. Again, centralization within a region would be preferable and would more rapidly lead to improvements (less observation/bed time). Where sufficient infrastructure exists, consent for additional biopsies could be rolled out to LDPs, using the LO consent and Patient Information Sheets, provided the biopsy material is transferred to the HTA-licensed premises within 7 days. Costs for additional biopsy needles, and for additional sample processing (since these would generate extra sample blocks), also need to be considered.

# Summary and Challenges

* **The transformational changes in pathology services which will be required to achieve the advances described here are likely to require top-down decree from NHSE**, redefining best practice in sample acquisition to achieve “modern” cancer diagnostics. Approval from the HTA (Human Tissue Authority) and HRA (Health Research Authority) will be required.
* Support from the Royal College of Pathologists, and key bodies such as British Society of Breast Radiology, British Society of Gastroenterology, British Thoracic Society, and others, will be essential.
* There is strong evidence that taking additional biopsies is associated with minimal risk and is acceptable to patients, but there are some resource implications.
* While change is being implemented, use of local Tissue Bank Biopsy consent processes may enable expeditious transition to biopsy collection in order to facilitate appropriate patients and samples to be recruited to the 100,000 Genomes Project Cancer Program, but this needs to be streamlined in order to integrate with the clinical diagnostic process. A proposed pathway is provided in the attached schema.
* Patient advocates are fully in favour of involvement in research in general, and in genomics research and precision medicine in particular. They agree that patients should be approached to consent to biopsies for research and there is wide agreement that a) biopsies are taken at time of diagnosis and b) there is a consent process until a genomic biopsy is accepted as standard of care.

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