# Consensus Statement

## Diagnostic pathways for NHS cancer genomic sampling and analysis

| Work stream | Participants | Status | Final |
|---|---|---|---|
| **Document Owner** | Clare Craig | **Version** | 1.1 |
| **Document Author** | See acknowledgements | **Version Date** | 20/03/2017 |
| **Release Approval** | Tom Fowler | **Approval Date** | 20/03/2017 |

# Contents



## Executive Summary

This joint statement from Genomics England and NHS England, endorsed by the Royal College of Pathologists, the Human Tissue Authority and Health Research Authority, outlines the view that tumour samples of sufficient size and appropriate nature for genomic and other molecular analyses can be taken and processed as routine diagnostic samples. This includes, for example, acquisition of fresh tumour samples taken for submission to the 100,000 Genomes Project. Precision cancer genomics is a dynamic and rapidly evolving field with an increasing diagnostic impact. Processing of samples for cancer diagnosis needs to reflect the different pathways for (a) molecular diagnostics and (b) histopathology. In addition, samples collected for routine clinical molecular diagnostics and the data these generate, may be used for subsequent research aimed at clinical benefit (with the appropriate informed consent and the necessary ethical approvals).

# 1 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. Furthermore, genomic analysis at the earliest stages in the diagnostic process should enhance the effectiveness of existing interventions. 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. **Thus, as molecular diagnostics become applicable to a wider range of patient samples, the systems and pathways for optimal handling of so-called 'genomic/molecular' tissue samples need to be established and embedded within the NHS.**

This consensus statement covers the principles of tissue sampling and uses the 100,000 Genomes Project as an example. Within the 100,000 Genomes Project, whole genome sequencing (WGS) is undertaken across a range of tumour types from NHS patients. Results are then returned to the patients via their clinical teams. The Project has brought to the fore the changes in clinical practice and sample handling that are required to embed this technology in the NHS, to establish WGS or more extensive genomic testing as standard of care for cancer diagnosis and to enable further NHS adoption of emerging new large-scale molecular technologies in the future (see appendix A). ). Cancer recruitment to the 100,000 Genomes Project has been limited, in part, by uncertainty about the need for Human Tissue Authority[1] licensing, under the requirements of the Human Tissue Act 2004[2] (see diagram).

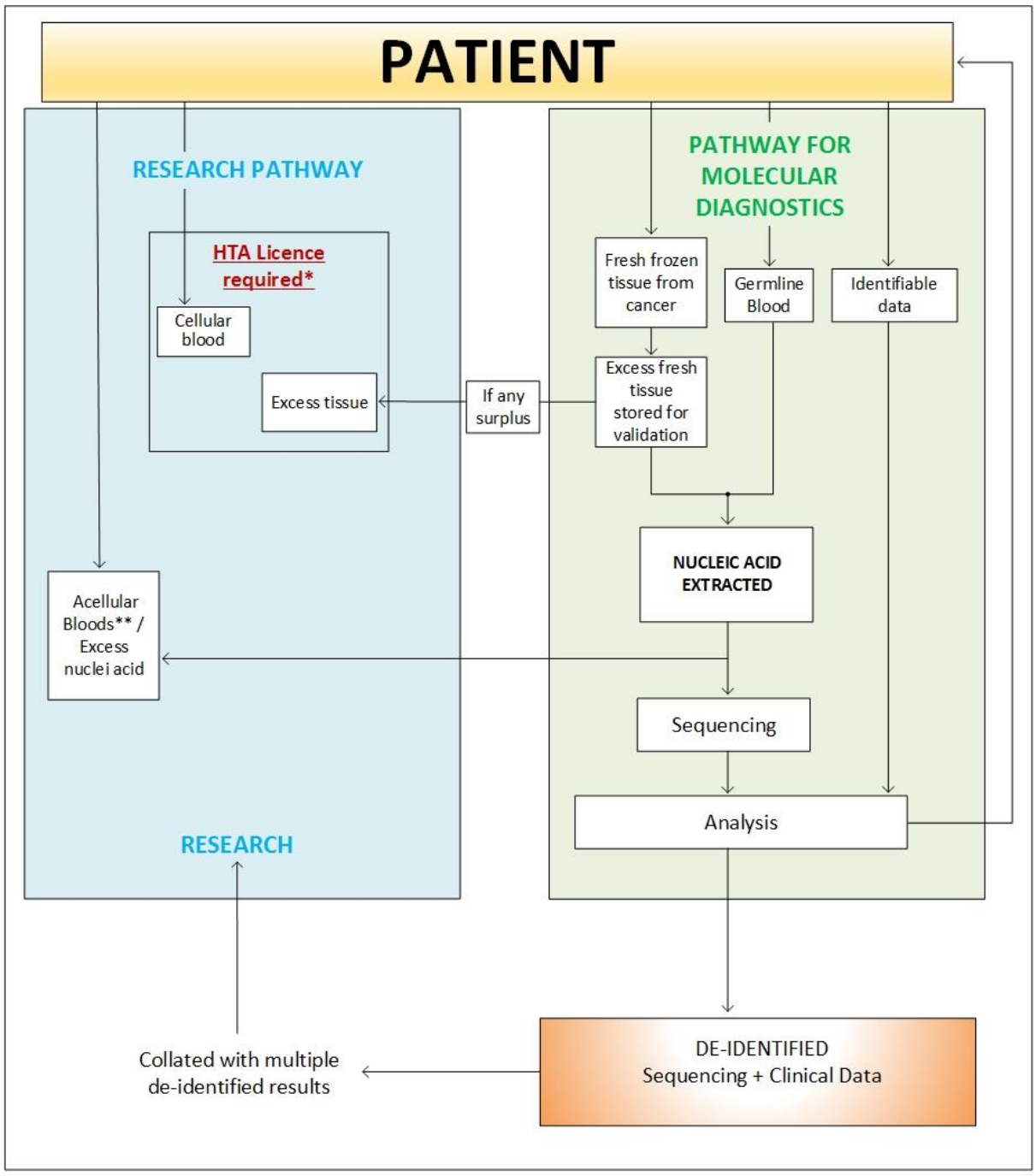
In the past, fresh frozen tissue has been predominantly used for research (rather than diagnostic) purposes, leading to uncertainty as to whether this cellular material could be treated as diagnostic, and therefore exempt from HTA licensing implications. When we introduced fresh frozen tissue samples for this Project there were a number of concerns from laboratories around legal implications. As large-scale molecular genetic analyses become increasingly clinically informative and affordable, acquisition and analysis of the appropriate tissue (which may include fresh frozen tissue) needs to be incorporated into pathological diagnoses. Establishing the fresh tissue diagnostic pathways for the 100,000 Genomes Project, and recognising this via this consensus document, is the first step towards achieving that future.

[1] Information about licensing requirements is available from the HTA https://www.hta.gov.uk/guidance-professionals/licensing-information

[2] Human Tissue Act 2004, applicable in England Wales and Northern Ireland. https://www.hta.gov.uk/policies/human-tissue-act-2004

## 2 Illustration of diagnostic and research pathways in the 100,000 Genomes Project

**Illustration of diagnostic and research pathways in the 100,000 Genomes Project**




*to store cellular material for research
**double spun/plasma only particular protocols render these blood samples acellular (see latest draft of Genomics England Sample Handling Guidance)

## 3 Principles of transforming NHS cancer sampling

High quality tissue samples are at the core of diagnosis, both morphological and genomic, and tissue must be handled appropriately for the test of choice. Historically, fresh frozen tissue was only collected for research purposes. A cultural shift is required to acknowledge that fresh tissue now has an important role in diagnostic testing in some circumstances, such as for WGS in the 100,000 Genomes Project.

There are a number of high-level principles that over-arch the implementation of molecular diagnostics as standard care for cancer:

- Molecular pathology and genomic analysis (of some breadth) will become standard practice in the analysis of cancer tissue samples.[3] Consent for tissue collection and licensing for the storage of this tissue in NHS diagnostic laboratories should reflect that cancer tissue and germline bloods are collected as part of standard care.
- Sample acquisition, sample handling and the sample pathway may need to be modified to ensure that 'genomic/molecular' samples are as high quality as possible, adequate and fit-for-purpose to ensure optimal molecular diagnostics. **For whole genome sequencing and other large-scale molecular genomic analyses, it is well established that analysis of fresh (frozen) tissue yields genomic analyses of substantially higher success and accuracy than formalin fixed, paraffin embedded (FFPE) tissue.**
- Although WGS may be the gold standard genomic test for all future tumour molecular analyses, in the short term there will be a mixed testing repertoire ranging from
    - -WGS in some selected patients, to
    - more extensive cancer gene panels for most patients, to
    - single genes where it informs immediate point of care decision making.
- In some of these testing scenarios FFPE is usually of sufficient quality. The principles in this statement apply to genomic and molecular analyses in general, covering single genes, panels, whole genomes and expression analyses. For many of these tests, optimal sample processing pathways differ to those used to prepare specimens for histology. Flexibility in tissue handling to fulfil different diagnostic requirements is imperative.
- Additionally, in this rapidly moving field, administration of therapies in an 'experimental' context is typical within everyday clinical management in oncology (as part of a randomised trial, an adaptive/basket/umbrella trial, in Phase 1 or via compassionate/early access programmes). Therefore, it should be considered part of standard care to collect tissue and undertake relevant molecular tests in a way that will enable clinicians to select the best available therapy options for their patients (with the appropriate informed consent).
- It should be anticipated that samples collected for, and data generated from, routine clinical cancer diagnostics may subsequently be used for research aimed at clinical benefit (with the appropriate informed consent).

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IMPROVING OUTCOMES THROUGH PERSONALISED MEDICINE https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf

# 4 Consensus position

## 4.1 Standard care includes the option of fresh tissue molecular diagnostics

NHS England intend to embed molecular pathology and genomic diagnostics as part of standard patient care. On this basis, collecting 'genomic/molecular' samples in an optimal manner for molecular diagnostics (when required), should be considered standard clinical care and part of the diagnostic pathway for patients with suspected cancer so long as it does not compromise the normal diagnostic approach for cancer. Where technologies require fresh frozen samples, as in the case of WGS in the 100,000 Genomes Project, then this also should be considered standard care, when the size of the biopsy permits and there is no risk of infection to laboratory staff.

## 4.2 Justification of diagnostic status for samples

**Definition of diagnostic:** A diagnostic test could broadly be defined as any test which helps identify or classify a disease. By this definition any test that gives more detail about a disease which may impact prognosis would be a diagnostic test. Any information that relates to a particular patient and their disease is diagnostic. Note that many 'diagnostic' biopsies will be taken to establish whether or not the patient has cancer; in the absence of an established diagnosis, priority for use of the tissue should be given to clarifying the nature of the disease.
**Definition of research**: Research information relates to the disease but not to any particular patient.

Because of the harmful effects of radiation, radiologists have redefined diagnosis tests to be tests to be those that have the potential to impact on a patient's treatment. The activity of molecular pathology does not cause analogous physical harm to patients, yet we have chosen to use the more stringent definition in this statement.

The evidence that 'genomic/molecular' samples are diagnostic, is given below and includes:

1. Impact on patient treatment
2. How clinicians treat the samples and results
3. Patients' perception of the testing

### 4.2.1 Impact on patient treatment

Genomic sequencing of cancer tissue provides three types of information. These can all influence patient care:

1. *Information that can directly impact on the choice, timing and duration of treatment*
    a. Choice of treatment
        i. Identification of a gene mutation that can predict a good response to a treatment. The treatment may be licensed or off-license
        ii. Identification of currently un-actionable mutations. This will enable open and informed conversations with patients about interventions that may or may not be available.

    b. Timing of treatment
        i. Identification of a mutation that informs prognosis. This may influence recommendations on choice and duration of standard chemotherapy.
        ii. Identification of a mutation that can be used to monitor early recurrence in order to decide when to start a further course of treatment.

2. *Suggestions for other treatments (where there is no evidence in that tumour type)*
    a. Information from sequencing can establish the patient's eligibility for taking part in a future clinical trial. If they are invited patients can freely decide whether or not to consent to joining such a trial.

3. *Information that we do not yet understand the relevance of*

This information may be useful in the future for that particular patient. It is therefore part of their diagnosis and must be kept as part of their diagnostic record for future reference. Also the de-identified data can be used in approved research.

*When are treatment decisions based on genomics?*

If a patient relapses after surgical resection (months or even years later), or presents with advanced or metastatic disease, a standard care first and/ or second line chemotherapy regimen is given for certain tumour types where there is evidence of efficacy. This may include licensed molecularly-targeted drugs. If there is no standard of care chemotherapy and/or the disease continues to progress despite exhaustion of standard-of-care drugs, the patient may be offered a clinical trial or a drug off-licence based on their genomic profile. This is typically a drug that has effective in a different tumour type, and can be accessed via the Cancer Drugs Fund. In the rapidly moving field of medical oncology, enrolment of patients in clinical trials and use of off-licence drugs is routine practice in the management of oncology patients. Many oncology patients receive life-extending therapy through this route.

*Using the first sample as a baseline*

In a given patient, the results from genomic profiling of current cancer tissue samples acts as a baseline to compare with genomic profiling performed on subsequent recurrent samples. Without this baseline sample, interpretation of the genomic profile of subsequent samples is more speculative. Serial whole genome analysis (WGA), including WGA from chemotherapy-naïve diagnostic biopsy followed by WGA from the metastatic sample, is particularly valuable to best inform drug selection. Using both reveals clonal evolution and molecular responses to prior treatment which aid decision-making.

*Impact of turnaround time on clinical decision making*

Currently, results from cancer whole genome sequencing in the 100,000 Genomes Project are not returned in time to inform decision making about initial treatments. Faster turnaround time for results will be achieved as the project infrastructure and processes matures. However, WGA can still inform clinical decision-making. For example analysis of a diagnostic biopsy or surgical resection may help to inform disease management and identify suitable drugs at the time of subsequent relapse. This may be months or even years after the diagnostic biopsy or surgical resection. Therefore, this information can be diagnostically relevant to patients regardless of when they receive it.

### 4.2.2 How clinicians treat the samples and results

**Fresh Frozen tissue as the superior tissue for Whole Genome Sequencing**

Two sources of information contribute to cancer diagnosis: histological and molecular. Formalin fixation and embedding in paraffin (FFPE) is well-established as the processing pathway that best facilitates histological (microscopic) analysis to assess tissue morphology and provide histological diagnostic information that establishes whether or not a patient's problems are due to cancer.. However, these chemicals degrade the tissue of nucleic acids (DNA and RNA) and induce artefactual mutations. Although DNA can be extracted from FFPE-processed tissue and it may be useful and sufficient for some molecular tests, the quality of WGS in the 100,000 Genomes Project has been

consistently inferior on material derived from FFPE tissue, compared to Fresh Frozen (FF) material. Particularly for WGA in the 100,000 Genomes Project, molecular (genomic) diagnostic information is best derived from fresh (frozen) tissue (FF) not subjected to chemical damage. In the future, full cancer diagnostics may require obtaining enough tissue to provide both optimally-processed 'histological' samples (typically FFPE) and additional tissue for optimally-processed 'genomic/molecular' samples (typically FF).

**Current tissue handling pathways**
It is important to note that fresh tissue sampling for molecular analyses and clinical diagnostics has been undertaken for clinical diagnostics in the NHS for some time. The approach is often used when testing for specific mutations in specified genes. However, to date fresh tissue sampling for diagnostics is only routine practice in a few centres, used on a small scale in a minority of NHS cancer patients for select tumour types. Nonetheless, the pathways are up and running within the NHS. Thus, where appropriate, the curation of FF samples should be sought, and considered part of the diagnostic process.

**Changes to pathways in NHS Genomic Medicine Centres**
To enable high quality genomic sequencing in the 100,000 Genomes Project fresh tissue samples need to be taken for freezing (instead of putting all tissue samples into formalin), or controlled, optimised fixation. This change in pathway does not preclude the use of material for a breadth of DNA or RNA diagnostic testing. All thirteen NHS Genomic Medicine Centres in England have already adopted this pathway in order to improve diagnostic yield from the 100,000 Genomes Project.

**Clinical validation of results**
When results from cancer whole genome sequencing are made available, they go through a number of quality control checks. The final check is a diagnostic, clinical check whereby a clinician at a local NHS site ensures that the whole genome sequencing concurs with other clinical and pathological findings. This includes individual gene sequencing. Therefore there is a need to keep sample material of the highest quality for this local validation. Stored material may also be required for important future analyses that are subsequently recognised as important. Accordingly, facility for long-term storage of fresh tissue within the diagnostic setting may need to be expanded.

### 4.2.3 Patients' perceptions

Following consultation with cancer patient representatives, these are some informative patient perspectives:
Cancer patients expect everything to be done to ensure that their precious tissue samples are handled to ensure optimal diagnostic information for their cancer management. They expect this handling to evolve over time, based on the changing tumour biology and emerging findings from studies around the world. If e.g. fresh frozen tissue handling achieves the best result, patients expect this to become routine, provided that it does not compromise the diagnosis of cancer. This premise applies for patients in the 100,000 Genomes Project and more broadly around NHS handling of their tissue. Patients have no concerns about their samples waiting for

a. Further clinical information to become available to demonstrate eligibility
b. More detailed consent for a particular project to be taken
c. Centralising of sample handling and processing for optimal outcomes

Many patients also want their own treatment experiences to bring broader benefits to others, which may include sharing data for research purposes (as evidenced by the Genetic Alliance UK's patient charter on cancer patient perceptions).[4]

## 5 Consensus statement

**The Human Tissue Authority (HTA) and the Health Research Authority (HRA) confirm that:**

- → In recognition of the increasingly routine role of molecular diagnosis in cancer care (since the original REC approval to begin the 100,000 Genomes Project in 2015), the definition of **diagnostic samples has been expanded** to include samples that have been removed, prepared and stored **so as to optimise molecular diagnosis.**

- → Therefore, samples pertaining directly to NHS diagnostic care i.e. fresh frozen tumour samples (previously considered a 'research' treatment of the samples because not used in diagnosis) and the taking of germline samples, are now considered to be **diagnostic samples for HTA licensing purposes.** Diagnostic samples do not fall under the Human Tissue Act 2004, therefore their storage in the NHS does not require any HTA licensing. Likewise tissue samples taken from a sample that is being stored for diagnostic investigation, have no HTA licensing implications associated with their storage, provided they are for diagnostic use in future. Many hospitals store residual fresh tissue as part of the diagnostic archive for validation or further diagnostic testing in the future, which have no licensing implications.

- → After 100,000 Genomes Project consent, participants' samples taken prospectively to support the diagnostic function of the 100,000 Genomes Project would also be exempt from HTA licensing in view of their diagnostic purpose.

  However, the above does not compromise or alter the requirements for the NHS or others to adhere to the HTA licensing and other obligations for storing cellular **research** samples, or from the point at which a relevant sample is considered to have **become a research sample**.

- → **The status of a relevant sample under the 2004 Human Tissue Act, may change according to its use.** Germline and cancer samples with a diagnostic use are considered diagnostic, until diagnostic studies are completed and any surplus material is **to be stored and used for research purposes**. For example, from the point a diagnostic purpose is completed and a cellular sample is stored only for research, the relevant HTA licensing for research will be applicable. Where HTA-licensed research tissue banks are subsequently to be developed using these samples, consideration should also be given to making a voluntary application to the HRA for ethical review and approval of a bank's arrangements for the collection, storage and release of material.

- → In the 100,000 Genome Project, tissue is collected then processed at NHS Genomic Medicine Centre hubs. Longer term (when the relevant sample is designated for research purposes only) it is stored as part of a central biorepository, the UK Biocentre, which is an HTA licensed tissue bank.[5] If research samples are being temporarily held in transit prior to DNA extraction, while being conveyed from one site to a HTA-licensed storage site, then this type

[4] 'Patient Charter: Genome Sequencing: what do cancer patients think?', Genetic Alliance, 2016 https://www.geneticalliance.org.uk/media/2493/my-cancer-my-dna-patient-charter-edits-sept2016.pdf

[5] https://www.genomicsengland.co.uk/taking-part/the-process/samples/

of storage is exempted from HTA research licensing if it is to be for 'a matter of hours or days and no longer than a week'[6]. Further guidance is available from Genomics England and the HTA.[7]

→ In the 100,000 Genomes Project, samples of centrifuged plasma for circulating tumour DNA and extracted DNA or RNA are acellular when processed according to Genomics England guidance[8]and therefore do not fall under the provisions of the Human Tissue Act 2004.

## 5.1 Benefits of the consensus statement

Adoption of the consensus statement (given below) will remove unnecessary ambiguity and local variation in handling fresh frozen tissue for clinical molecular analyses in the NHS, contributing to clinical diagnostics and patient benefit.
The statement clarifies regulatory expectations around HTA licensing for storage of this tissue, supporting recruitment to the 100,000 Genomes Project. Furthermore it supports clinical molecular diagnostics in general as well as other translational initiatives, such as molecularly-stratified trials where required.

**Specifically in relation to the 100,000 Genomes Project:**

- Subject to consent to participate in the 100,000 Genomes Project[9], samples previously collected from cancer patients for clinical care purposes in the NHS, may be included in the 100,000 Genomes Project, provided these are in line with the Genomics England's sample handling guidance where the appropriate consents are in place

- The 100,000 Genomes Project mainly collects samples that have a potential *dual use*: firstly in diagnosis and subsequently for future research using any material surplus to diagnostic need. The Project also collects some additional blood samples which are optional and *solely* have a future research purpose (at present). This latter category is expected to include fewer examples over time as NHS genomic medicine develops. The 'diagnostic' label is likely to expand further to encompass more types of information and samples.

- There has been some reluctance from NHS tissue collection sites *without* a Human Tissue Authority (HTA) research sector licence, or who do not know what, if any, HTA licensing has been applied to their site, to participate in the 100,000 Genomes Project. This is due to reasonable concern that they may be handling research samples inadvertently. The consensus position would give these sites clarity around participation in the 100,000 Genomes Project. Perhaps most importantly it would remove diagnostic inequality between patients, by maximising the NHS storage and use of fresh frozen tissue samples, which are the optimal form for subsequent whole genome analysis.

[6] see HTA website, Licensing exemptions 'Tissue being held prior to processing' https://www.hta.gov.uk/policies/licensing-exemptions
[7] Guidance from HTA on storage of samples for research: https://www.hta.gov.uk/guidance-professionals/codes-practice/code-practice-9-research

[8] Current 100,000 Genomes Project sample handling guidance: https://www.genomicsengland.co.uk/information-for-gmc-staff/sample-handling-guidance/

[9] 100,000 Genomes Project participant information and consent forms available here: https://www.genomicsengland.co.uk/taking-part/patient-information-sheets-and-consent-forms/

- Adopting the consensus position avoids the need for centres to manage samples as research samples, as a precaution, where this is not needed

# 6 APPENDIX A

**The 100,000 Genomes Project**

The 100,000 Genomes Project is being delivered by Genomics England and NHS England in partnership with 13 NHS Genomic Medicine centres in England. The Project invites patients with eligible cancers or rare inherited diseases and their relatives, to donate biological material in order for their germline DNA (plus the genome of their cancer, as relevant) to be analysed.

It is hoped that this analysis will give clinicians a better understanding of mechanisms of disease and help to transform future diagnosis and treatment. The Project enables the NHS to offer diagnostic genome sequencing for patients with cancer, beyond that offered as a current standard of care. The project also has research aims and makes de-identified genomic information and other health information available to approved researchers in a specific secure, monitored online environment.

This means that the Project is not itself a research study, and does not constitute research under the Research Governance Framework (RGF), instead facilitating the future research of others.

The 100,000 Genomes Project also aims to inform clinical care by returning results about a patient's cancer or rare disease gathered from their sequence data combined and other health data. These results are ultimately being fed back to the participant via their clinical team.

Furthermore, the Project offers potential direct clinical benefit to participants via its 'additional findings' offer. This (optional) activity looks for genomic changes known to cause serious, life threatening conditions or an increased risk of certain genetic diseases, which if identified, can be prevented or reduced by NHS treatment. We expect that only about 1 in 100 people who take part will have one of these conditions. Genomics England only look for these changes if a participant gives us explicit consent to do so.

**Samples taken**

In addition to tissue samples taken from surgical resections, biopsies or aspirates of cancer tissue other samples are also taken for the project:

*Germline samples*

To interpret the genome sequence for cancer samples, a germline blood sample is needed to compare the cancer genome to the normal genome. Occasionally an alternative cellular sample e.g. saliva, will be taken instead, such as in the case of blood cancers. These samples are required in order to allow the cancer tissue samples to be diagnostically interpretable. Therefore they are diagnostic themselves.

*Other blood samples*

As part of the 100,000 Genomes Project peripheral blood samples are taken for circulating free tumour DNA. By monitoring circulating tumour DNA a recurrence can be spotted. This allows treatment to commence before a recurrence has become larger and harder to treat. Given the impact on treatment these samples are considered to be diagnostic.

Optional blood samples are also taken for further testing of RNA, protein and metabolite levels in the blood. These samples may or may not have a diagnostic impact and at this stage these are considered to be research samples. Some of these samples are whole blood samples and HTA licensing would be required to store these samples for research 'in connection with disorders, or the

functioning, of the human body'. If samples are being temporarily held in transit, while being conveyed from one site to a HTA-licensed storage site, then this type of storage is exempted from HTA licensing if it is to be for a matter of hours or days and no longer than a week. Further guidance is available from Genomics England and the HTA [insert link].

Other samples are acellular centrifuged samples which are not considered to be 'relevant material' as set out in the Human Tissue Act 2004.

*Turnaround times*

Turnaround times for return of analyses to the clinical team from 100,000 Genomes Project are currently not established and reproducible. Accordingly, WGA cannot currently be used as a routine test to inform first-line clinical decision making. This is explained to participants in the consent discussion and participant literature. Nevertheless, as a pilot study, we have expedited three samples for patients with metastatic disease on a 'compassionate' basis. The results were returned in ~ 6 weeks and were used 'real-time' to select treatments for those patients. We are aiming to reduce turnaround times over the course of the project to expand the potential benefits of using WGA for 'real-time' clinical decision-making. Never-the-less, as outlined above, the diagnostic information received from WGA impacts on other aspects of patient care.

**Research Ethics approval and Human Tissue Authority (HTA) licensing obligations in the 100,000 Genomes Project**

Research ethics governance is in place for the 100,000 Genomes Project via independent HRA REC approval and scrutiny (REC REF 14/EE/1112) and Genomic England's corporate governance, including the Ethics Advisory Committee which advises the Board of Directors of Genomics England.

The Project is a research tissue bank, offering a consent which combines research and clinical aims, allowing human biological material to be collected, transferred, stored and processed in order to establish a genomic dataset for the benefit of future research. In 2015, when the project was established the HRA REC's opinion was that the samples in the cancer arm of the 100,000 Genomes Project could not be considered diagnostic and so cancer samples should be treated as research samples, with the attendant HTA licensing implications. This document recognises that subsequently such samples are being considered diagnostic in nature.

## 7 Acknowledgments

We would like to thank the following colleagues for their valuable contributions:

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|---|---|
| Dr Clare Craig | Genomics England |
| Laura Riley | Genomics England |
| Tom Billins | Genomics England |
| Dr Louise Jones | Genomics England |
| Dr Tom Fowler | Genomics England |
| Dr Clare Turnbull | Genomics England |
| Dr Nirupa Murugaesu | Genomics England |

| | |
|---|---|
| Dr Jo Mason | Genomics England |
| Prof Mark Caulfield | Genomics England |
| Dr Jane Moorhead | NHS England |
| Prof Sue Hill | NHS England |
| Dr Suzy Lishman | Royal College of Pathologists |
| Prof Tim Helliwell | Royal College of Pathologists |
| Prof Ian Cree | Royal College of Pathologists |
| Prof Finbarr Cotter | Royal College of Pathologists |
| Christopher Birkett | Human Tissue Authority |
| Fiona Maleady-Crowe | Human Tissue Authority |
| Prof Nalin Thakker | Health Research Authority |
| Joan Kirkbride | Health Research Authority |
| Prof Lucy Raymond | East of England NHS GMC |
| Prof William Newman | Greater Manchester NHS GMC |
| Dr Paul Brennan | North East and North Cumbria NHS GMC |
| Prof Lyn Chitty | North Thames NHS GMC |
| Dr Angela Douglas | North West Coast NHS GMC |
| Dr Anna Schuh | Oxford NHS GMC |
| Prof Sean Whittaker | South London NHS GMC |
| Prof Sian Ellard | South West NHS GMC |
| Prof Karen Temple | Wessex NHS GMC |
| Dr Anthony Williams | Wessex NHS GMC |
| Prof Kikkeri Naresh | West London NHS GMC |
| Prof Dion Morton | West Midlands NHS GMC |
| Dr Andrew Mumford | West of England NHS GMC |
| Dr Andrew Jack | Yorkshire and Humber NHS GMC |