**Royal College of Surgeons**

**Commission on the Future of Surgery: the impact of genomics**

**Evidence submitted by the Chief Scientist's Team at Genomics England.**

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**Contents**

## 1. Introduction

The Chief Medical Officer's annual report, Generation Genome, emphasises how genomic medicine has the potential to save costs and improve quality of care by stratifying and targeting treatment, maximising benefit and reducing side effects [1].

Developing comprehensive, co-ordinated and consistent genomic testing as standard of care is key to the delivery of high quality cancer care across the UK and in line with NHS England's Five Year Forward View. The framework and timeline for genomic-led personalization of treatments and interventions in the NHS were set out in 2015 [2], and in 2017 NHS England approved creation of a comprehensive NHS Genomic Medicine Service. This will comprise a genomic multidisciplinary team, of which surgeons will be key members, supported by genomic laboratories and IT infrastructure to integrate genomic testing into patient management, from diagnostics, through to treatment decisions based on a greater understanding of the molecular profile of tumours. The expansion of genomic analysis has already and will continue to transform multiple aspects of surgical practice, including changes in tissue handling to ensure optimal sample quality, planning of patient care incorporating predictive and prognostic testing, multidisciplinary interpretation of molecular analyses at Tumour Boards, and an appreciation of the ethical framework around genomic testing and the evolving nature of the consent process in this context. Genomic testing is also likely to impact on approaches to cancer screening, both in existing screening programmes and potentially offering opportunities for cancer types with no current screening.

In this paper, we outline the areas that will be influenced by the growth of genomic testing, drawing both from published evidence and experience in delivering the 100,000 Genomes Project, and we advance the concept of the Genomic Surgeon as the champion and guardian of this modern care pathway.

## 2. Tissue Handling

The long-established process of formalin fixation and paraffin embedding (FFPE) of tumour samples significantly damages DNA. Whole genome sequencing (WGS) on FFPE samples

generates large numbers of both false positive and false negative results, as explained further in Appendix A. Experimental work has shown that even with 'optimised' formalin-fixation protocols, the quality of WGS data is significantly compromised, driving the need to obtain fresh or fresh-frozen tumour samples to give optimal WGS results [3]. There are other potential benefits in handling tissue fresh followed by controlled fixation: pre-analytical factors such as fixation time can have a major impact on outcome of immunohistochemistry [4], and in an area where predictive IHC, such as for PDL-1, is rapidly evolving, controlled tissue handling becomes increasingly important. Changes in tissue handling require a significant re-engineering of the diagnostic cancer pathway to optimise and standardise tissue handling in order to achieve high quality molecular testing whilst retaining morphology for diagnosis.

This already is beginning to impact on surgical practice with surgeons across the country now responsible for ensuring that diagnostic material is kept fresh or additional fresh material is taken in parallel with conventional sampling. Surgeons also are helping to ensure that surgical resection samples can be refrigerated in theatres, with or without vacuum packing, to allow for successful whole genome sequencing.

**Formalin-free theatres**

Recognition of the improved quality of fresh tissues samples for genomic analysis and the benefits of more standardized controlled fixation is driving the broader discussion of removal of formalin, from operating theatres and other settings [3].

In 2013 the EU-REACH adopted a decision to reclassify formaldehyde as a Cat. 1B carcinogen and Cat. 2 mutagen under the EU CLP Regulation and an EU Directive from the European Chemical Agency in January 2016 has classified formalin as a Category 1B carcinogen [5]. This legislation makes the employer responsible for minimising staff exposure to formaldehyde and formalin.

Hospitals that have removed formalin from theatres and substituted refrigeration which has identified other benefits including, reduced weight of samples for handling by staff; reduced bulk for transportation and storage; costs saved on purchasing formalin, along with cleaning, disposal and sampling fresh tissue for genomics [6].

Surgeons are the custodians of surgically excised tissue until its safe delivery to Pathology, and as such they are invested in ensuring that the tissue is handled optimally in order to give high quality downstream assessment – morphological, biological and genomic – since this ultimately impacts on the integrity of the information that surgeons use to plan on-going management. Thus surgeons will need to drive these changes in practice, working closely with their operating theatre teams and with pathology departments to ensure robust pathways are established that offer the best standard of care.

A number of surgical and pathology teams across the UK are already trialling sample refrigeration or vacuum-packing. To achieve this change on an NHS-wide basis will require a strong evidence-base of best practice. The Royal College of Pathologists have set up a working group to assess the process for removal of formalin from theatres on which surgeons will be represented, and NHSE are co-ordinating the sharing of evidence across the NHS Genomic Medicine Centres to inform the implementation of these new pathways.

**Surgeons will drive the implementation of optimal tissue handling as custodians of patient samples and with investment in the quality of downstream analysis. They will educate their theatre teams in handling fresh samples and ensuring rapid refrigeration with or without vacuum-packing and in doing so will be central in driving up sample quality and subsequent impact of quality of care.**

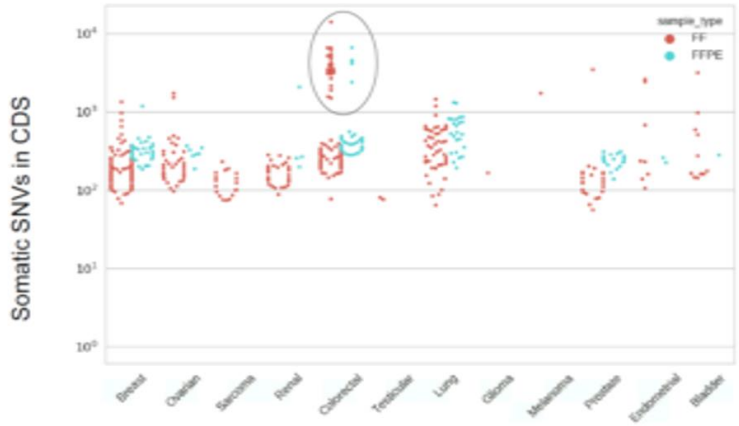
**Somatic Variants in 472 Cancer Patients (Red = fresh tissue and blue = FFPE)**

Number of somatic small variant calls per normal-tumour pair – exomewide.

Elevated number of somatic variant calls in colorectal cancer samples.

Observed in both FF and FFPE samples.

We expect 15% of colorectal cancers to have defects in the mismatch repair pathway.




### 3. Ethical considerations and the evolution of Consent

As with the introduction of any new technology into the clinical setting there must be an awareness of the ethical implications of expanded genomic analysis for cancer patients. Genomic analysis for certain target genes in specific cancer types already is standard of care, for example, Her2 testing in breast cancer, EGFR and ALK mutation status for types of lung cancer [6,7]. These tests are accepted as being of benefit to the patient, opening potential therapeutic opportunities, so maximising quality of care, and as such no specific consent is sought to undertake these tests. Within the context of the 100,000 Genomes Project, the analysed cancer WGS will highlight potentially actionable variants: some of these will be recognised variants pertinent to that tumour type with established NICE-approved therapies in place; others may be potentially targetable variants not currently licensed for treatment in that cancer group. Since interpretation of cancer WGS also requires germline WGS, additional findings may be uncovered with important or uncertain implications for the patient beyond their immediate cancer care.

Participation in the 100,000 Genomes Project entails taking fully informed consent to cover taking data to be held centrally as well as sharing the de-identified clinical and genomic data for research. However, there are certain tumour subgroups, such as haematological malignancies and some sarcomas, where the breadth of potentially actionable and predictive of prognosis variants has expanded [9,10] such that WGS provides a 'one-stop' single platform

test to provide the full gamut of information relevant to these patients, and the adoption of this approach as standard of care may be imminent. As the infrastructure for molecular testing within the NHS becomes established and the range of molecular tests for other cancers starts to increase, there likely will come a point where adoption of a single platform for all tests, such as WGS, will become the most efficient and cost-effective approach.

Surgeons are frequently the first and major interface with patients at the time of diagnosis and planning care. As the plethora of genomic analysis expands it will be essential for surgeons to have a comprehensive understanding of the ethical implications of such testing for their patients, including an understanding of the limitations and uncertainties intrinsic to some molecular analyses, such as detecting variants of uncertain significance.

As key communicators with patients, surgeons will need to be fully cognisant of the true and perceived issues around molecular testing, so they can appropriately inform and guide their patients with the same level of skill and knowledge with which they advise on surgical procedures.

**Consensus Statement: Diagnostic Pathways for NHS Cancer Genomic Sampling and Analysis**

Whilst informed consent is required to carry out WGS on patient samples, the recognition that molecular analysis of patient samples requires the highest quality material for robust results, and the growing potential for such testing to become standard of care when clinically indicated led to the development of the Consensus Statement [11].

Here, the Royal College of Pathologists, the Human Tissue Authority, the Health Research Authority, NHS England, Genomics England and representatives from NHS Genomic Medicine Centres came together to issue a joint statement that collection of fresh tissue samples and blood for potential molecular analysis can be considered as standard of care for cancer diagnostics. This statement facilitates the availability of samples that will give optimal results for genomic analysis where such tests are deemed appropriate. It recognises the emergence of cancer molecular diagnostics as routine practice and lays down an infrastructure where such sampling is routine.

**Surgeons are key communicators with patients around their planned management. As such they will need to have the knowledge and skills to outline the benefits, limitations and potential uncertainties associated with different types of molecular testing, and to understand the evolving accepted practice in undertaking such testing.**

## 4. Planning Patient Care: Molecular testing for diagnosis, patient stratifcation and precision care

To date, molecular testing in cancer has focused primarily on analysis of single or small numbers of genes to which there are existing targeted therapies, such as Her2 in breast cancer and EGFR in lung cancer, or which predict prognosis and therefore influence treatment decisions, such as the Recurrence Score derived from Oncotype Dx in breast cancer [12]. Large scale omic studies, embracing DNA and RNA sequencing as well as epigenomic and proteomic analysis across many tumour types have identified key drivers of cancer and new disease classifiers with prognostic and therapeutic relevance [13,14]. 'Mutational signatures' or patterns of alterations across the genome have been identified for different cancer types and some of these are being evaluated for their power to predict drug response and patient prognosis [15]. In addition to guiding medical management, molecular testing is likely to impact on surgical management. As surgical procedures increasingly aim to achieve conservation of organs, ensuring adequate clearance of margins becomes of central importance. The concept that molecular analysis may guide more accurate surgical excision is already being explored through initiatives such as the iKnife [16], which uses real-time mass spectrometry of electrosurgical aerosol to identify abnormal tissue at the site of cutting. The concept of field cancerisation – the presence of morphologically normal but genomically aberrant tissue around cancers is well established [17] and has been shown to influence rates of recurrence [18] such that future molecular approaches to assessing margins may further improve recurrence rates.

Advances in molecular technologies will also influence how patients are monitored: detection and characterisation of minute quantities of circulating tumour DNA (ctDNA) is showing great potential in the early detection of recurrent tumour, prior to clinical or radiological detection [19]. Advances in risk prediction are also likely to influence approaches to screening for

cancer, with algorithms designed to integrate multiple low-risk allelles into 'polygenic risk cores' to better stratify an individual to low and high risk; such approaches are already in clinical trials [20].

**Surgeons will need to refine patient management with improved stratification of care through the integration of molecular features of the tumour with conventional pathology and staging. As well as guiding medical management plans, adoption of molecular approaches to improve surgical care will become part of the clinical repertoire.**

5. **The new Genomic Medicine Service and the key role of the Genomic Surgeon in the multidisciplinary process.**

**The key role of the Genomic Surgeon in this multidisciplinary process.**

We see a key role for the Genomic Surgeon who deploys genomics to pre-screen patients, to identify successful cancer clearance and to detect relapse and maybe stratify therapy with the genomic molecular signature from a whole genome or panel test. The role of this Genomic Surgeon as a driver of change as this technology evolves will be to champion the use of optimal diagnostic sampling, to understand via education how the molecular signature of tumour DNA should be used and to communicate this to the patient. This will enable a smooth relay of the baton of care to the oncologist and radiotherapist based upon the utility of genome sequence in selecting tailored treatment for their patient. The surgeons as the initiator of the care pathway must become the champions of genomically friendly tissue handling and ensure that this information becomes the province of the many in cancer care and does not remain confined to a few clinical academics. Molecular Tumour Boards are being established across the UK for the interpretation and incorporation of molecular testing into the patient report, and to define the impact on the management plan. **Surgeons must play an integral part in this multidisciplinary process.** For best practice here in use of this information consult Prof Dion Morton in the University of Birmingham who has generalised cancer genomic medicine in the West Midlands.

The new NHS Genomic Medicine Service will be delivered in England via new Genomic Laboratory Hubs with Genomic Medicine Centres sending samples for testing. These hubs

assume responsibility for molecular testing in cancer care according to a new National Genomic Testing Directory. This Directory will define the appropriate genomic testing for different cancer types, ranging from single gene tests to panels to whole genome sequencing, thus exposing clinicians to the gamut of molecular tests. From October 2018 Genomics England, in partnership with NHS England, will concentrate all genomic tests in a single data centre for both patient care and research under informed consent. Genomics England will manage a whole genome sequencing and interpretation pipeline and industrial and academic collaboration. The time for professionals to adopt this and become adept at service delivery is now.

## 6. Conclusion

The potential of the genomics revolution to transform personalized medicine is a focus of healthcare systems across the world [21].

Genomic testing has been in use for cancer patients for many years with gene panel testing or FISH to look for variants or translocations that help with treatment decisions. Large scale omic studies have identified new disease classifiers and highlighted the potential to gain prognostic and predictive information to influence patient management. For patients, genomics holds the promise of: refining prognostic and predictive information and directing the most appropriate cancer care individualised to that patient.

The 100,000 Genomes Project has driven the development of a genomic testing infrastructure within the NHS. The moment to embrace Genomic Medicine is now and in the era of the NHS offering a National Genomic Medicine Service with a National Test Directory it will be vital that surgical care embraces this and seizes the moment to create the Genomic Surgeon, who as the usual initiator of this pathway, is the natural driver to the best genomically primed cancer care.

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**Appendix A**

**Effect of formalin on tissues**

During the 100,000 Genomes Project's Pilot and Initiation Implementation Phases, extensive experimental work was undertaken to optimise and standardise the process of formalin fixation and to adapt the DNA extraction process to minimise DNA damage. However, whilst there was some improvement seen, WGS on formalin fixed paraffin embedded (FFPE) tissue continued to be substantially suboptimal, leading to the conclusion that for optimal WGS fresh tissue is required.

Formaldehyde is highly reactive with DNA bases and proteins forming protein-DNA, interstrand DNA, and protein-protein crosslinking and DNA-formaldehyde adducts (Do & Dobrovic, 2015). The result is a combination of direct fragmentation, abasic sites and deamination of cytosine to uracil or thyamine causing false positive nucleotide variants. The consequence is generation of artefactual mutations (false positives), making the reliable detection of structural variants and mutational patterns such as signatures extremely difficult.

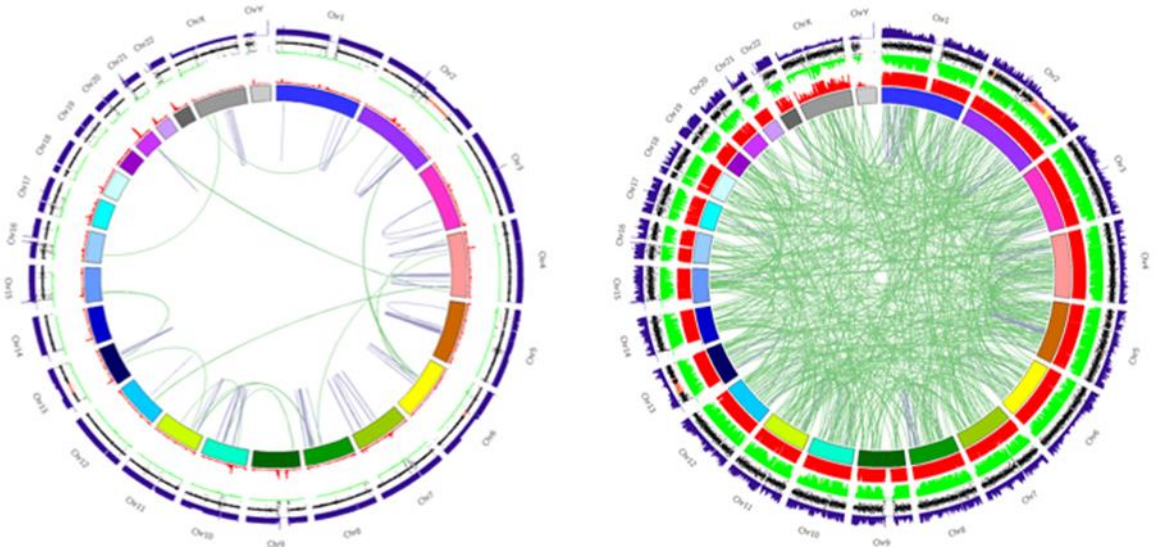

Figure 1: Artefactual mutations caused by formalin fixation. *This plot illustrates the distribution of somatic variants in a fresh frozen (FF) and FFPE sample from the same prostatic cancer across the genome. It shows the greatly increased number of mutations introduced due*

*to formalin-induced DNA damage. Chromosomes are arranged sequentially around the circumference as indicated. Structural variants (SVs) are indicated by arcs inside the plot; translocations are indicated in green, inversions are indicated in purple. Track 1 (innermost track): chromosomes; Track 2 (in red): number of somatic SNVs; Track 3 (in green): number of somatic indels; Track 4: ratio of normalised depth of coverage for tumour vs normal. CNV losses are indicated in red, CNV gains are indicated in green, copy-neutral LOH regions are indicated in yellow; Track 5 (outermost track, in blue): absolute depth of coverage in tumour sample.*