Professor Sue Hill
CSO England

Professor Mark Caulfield
Chief Scientist Genomics England

Ellen Graham
Deputy Director - Genomics

20th February 2018

Dear Sue, Ellen and Mark,

We are writing as representatives of the British Society for Genetic Medicine, its constituent societies, and the Medical Genetics Clinical Reference Group to welcome the opportunity to utilise new genomic technologies to deliver high quality clinical services to NHS patients.

We endorse the use of whole genome sequencing (WGS) in NHS diagnostics but also caution against the over simplification of the challenges we face in meeting this goal. We are committed to working with NHSE to meet our joint aims and therefore highlight some points for consideration:

1. **Errors arise when a test result at variance with the clinical presentation or family history is given too much weight, and/ or is regarded as a definitive diagnosis rather than one element in the process of diagnosis**. The introduction of WGS will alter the diagnostic pathway for many patients. Whilst this will shorten the "diagnostic odyssey" for some, for others, the lack of a clear phenotype/ strong family history will mean that interpretation of results from WGS will require additional investigations (e.g. biochemical testing, imaging, immunohistochemistry, testing of family members and clinical follow-up) to prove or disprove a diagnosis. These investigations may be expensive and their introduction within routine pathways has not yet been costed or evaluated. There is a risk that genomic results may be taken at face value by clinicians who have more limited genomic knowledge with a potential for misdiagnosis which would adversely impact both the patient and often the wider family. Whilst a genotype can provide a molecular diagnosis of an observed phenotype, a genotype alone often does not accurately predict a phenotype.

   The importance of high quality phenotyping and the need for access to clinical genetics/ multidisciplinary expertise to offer advice on the relevance of variants in a particular clinical scenario, remains highly relevant for any diagnostic genomics service.

2. **Utilising WGS for some diagnoses may mean that fewer WGS tests are available for the conditions where WGS is indicated.** Clinical Genetics is one of the mainstream specialities already utilising genomic medicine and has noted that in children with intellectual disability (cheaper) non-WGS based approaches currently diagnose up to 50% of this group. Just as a very high blood cholesterol level or finding of multiple cysts on renal ultrasound will still be a relevant investigation prior to WGS, so will selection of those children most likely to benefit most from the- still finite- resource of WGS. We await evidence from the 100,000 genomes project that we can use WGS as a first line test to diagnose disorders due to structural variants such as deletions and duplications, triplet repeat expansions or metabolic disorders.

   Until such evidence is robust, we recommend that suitable pre WGS tests are defined to appropriately target the still finite resource of WGS.

3. **More evidence about 'actionability' and clinical pathways are needed before additional 'looked' for findings are offered routinely.** This requires that there is evidence of clinical utility of interventions offered to individuals with variants identified as a result of a deliberate search in genes outside those indicated by the clinical reason for offering WGS. We endorsed the inclusion of additional findings (AFs) for a limited set of actionable mutations in genes in the 100,000 genome project as a research question. However, we consider that **evaluation and implementation research** into the impact of AFs needs to be done on the 100,000 cohort before it is offered as routine NHS practice. We are concerned, therefore, that no AF results are likely to be available before WGS transfers to the NHS and that no such evaluation has yet taken place. Whilst the ACMG have recommended the search for a much larger panel of AFs, there is very limited evidence about this and health care in the USA is not directly comparable with the genomic service planned for the NHS. The search for AFs within routine clinical practice could be compared with offering total body MRI scanning when a knee MRI is indicated.

   We consider that the generation and reporting of AFs is potentially harmful in a number of ways: (a) chance of over-diagnosis (including for example, referral for risk reducing surgery); (b) potential inappropriate reassurance since sporadic cases will far outnumber the rare heritable types; (c) results falling outside the expertise of the clinician requesting the test (eg cardiologist receiving a Lynch syndrome AF result). We are aware that some health professionals and patient representative groups erroneously believe that more genomic information will always be better than less, and that clear evidence and actions will follow from an AF. The reverse is the case: those with an AF may never develop clinical disease, and such asymptomatic carriers may require lifelong clinical follow up. This can substantially add to the overall burden, anxiety and potential harm to patients from unnecessary investigations and treatments whilst also increasing costs to the health service.

   Evaluation and implementation research into the impact of AFs needs to be done on the 100k cohort before it is offered as routine NHS practice. There are several groups nationally who could assist with this.

4. We also note the emerging evidence from the US (and the UK) which suggests that premature use of this technology by clinical services unfamiliar with it dramatically increase the chance of litigation. ***If this proves true then the overall cost of adopting WGS in mainstream medicine could impose significant NHS costs as well as patient dissatisfaction.***

Those working in applications of genetics in medicine in the UK over the past 30 years are internationally recognised leaders in the rapidly evolving field of genomics, and are enablers of the early adoption of a range of technological advances into clinical practice over this time. We hope that this combined expertise provides some helpful insights, which we offer in a spirit of collaboration aimed at developing the best service possible for the future of the NHS.

Yours Sincerely,

Anneke Lucassen- Chair, British Society for Genetic Medicine
William Newman- Vice chair, former chair, British Society for Genetic Medicine
John Dean- Secretary, British Society for Genetic Medicine
Dominic McMullan- Chair of the Association Clinical Genetic Science
Frances Elmslie- Chair Medical Genetics Clinical Reference Group
Jane Hurst- President, Clinical Genetics Society
Hilary Burton - Consultant in Public Health Medicine, PHG Foundation
Alison Hall- Chair Ethics and Policy Committee BSGM; head of Humanities. PHG Foundation,
Helen Firth- Academic Vice-President Clinical Genetics Society
Carol Gardiner- Chair, Fetal Genomics Group
Edward Blair- Clinical Lead Oxford Genome Medicine Centre
John Dean, Secretary, British Society for Genetic Medicine
Peter Marks- Chair, Association of Genetic Nurse Counsellors
Katherine Lachlan – Clinical Lead Wessex Clinical Genetics Service
Angus Dobbie- Chair Lead Clinicians Group
Lucy Side- Chair Cancer Genetics Group
Marc Tischkowitz- Secretary, Cancer Genetics Group
Ian Frayling- Treasurer, Cancer Genetics Group
Emma Woodward – Council member, British Society for Genetic Medicine
Angus Clarke- All Wales Clinical Genetics Service
Diana Eccles – Chair, British Breast Group
Karen Temple - Clinical Lead Wessex Genome Medicine Centre
Frank Jones - Public Patient Voice