Preparing Primary and Community Care in the NHS for Genomic Research: a joint report by the NIHR CRN and RCGP

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Preface

The new genomic revolution is predicted to impact on mainstream medicine and the heart of the NHS in the near future. The NIHR CRN has worked through its stratified medicine initiative to prepare the NHS for personalised medicine studies. However, it has become clear that primary and community care may not be as prepared for the advent of genomic medicine studies as other parts of the NHS.

Cluster C of the NIHR CRN, which is a cluster of clinical specialties based in Kings College, has been leading on this new initiative as part of its Emerging Technology and Innovation (ETI) activity. Work initially with Sir Munir Pirmohamed and the Pharmacogenetics and Stratified Medicine Network led to a joint meeting in November 2017. A report was produced and a Cluster C Steering Group was convened after discussion with key stakeholders. This Group (see below) met in January 2018 and agreed terms of reference.

Three key workstreams were identified and stakeholders in each workstream were approached. The NIHR CRN has worked in collaboration with the Royal College of General Practitioners (RCGP) on this part of the project and its joint Genomics Champions, Drs Hayward and Rafi.

This Report is the outcome of this collaborative project and contains recommendations from both organisations to promote genomic research in primary and community care and I hope that it will make a significant impact in this rapidly evolving area.

Philip Evans
Professor Philip Evans
Cluster C Specialty Lead
Kings College
London

Table 1: Membership of Primary and Community Care Genomic Research Steering Group

Professor Philip Evans CHAIR	GP and CRN Primary Care National Specialty Lead / KCL Cluster Lead
Dr Imran Rafi	GP and Joint Medical Director CIRC, RCGP
Dr Jude Hayward	GP and Primary Care Adviser to Health Education England Genomics Programme
Professor Hilary Burton	PHG Foundation Officer for England, NHS England
Dr Alex Henderson	CRN Genetics National Specialty Lead
Helen Macdonald	Research Delivery Manager, CRN Eastern
Professor Nadeem Qureshi	GP and Clinical Professor of Primary Care, University of Nottingham
Dr Mariam Molokhia	GP and Reader in Epidemiology & Primary Care, KCL
Professor Sue Hill	NHS Chief Scientific Officer, Senior Responsible Officer for Genomics NHS England
Professor Lyn Chitty	Professor of Genetics and Fetal Medicine, UCL and Clinical Director for North Thames LCRN
Professor Christine Patch	Reader in Genomic Healthcare, KCL
Professor Richard Trembath	Executive Dean of the Faculty of Life Sciences and Medicine, KCL
Professor Eamonn Maher	From July 2018 (Replaced Dr Henderson) CRN Genetics NSL Professor of Medical Genetics and Genomic Medicine, Cambridge
Professor Dyfrig Hughes	From June 2018 - Professor of Pharmacoeconomics, University of Bangor

NIHR CRN KCL Cluster Representative(s):	
Joanne Ashcroft	KCL CRN Assistant Specialty Cluster Lead
Dr Jo Mearhart	KCL CRN Cluster Manager
Joy Choules	Admin support

The process

As described in the preface, following the initial steering group meeting, three workstreams were established and key stakeholders were identified for each of these workstreams (see lists in Appendix 1). Two workstream teleconferences were held on 8 May and 26 June 2018 and chaired by the individuals detailed below:

1. Informatics relating to genomic research in primary care (Prof Philip Evans - 26 June)
2. Operationalising Genomics Research (Dr Imran Rafi - 8 May)
3. Developing the Genomics workforce (Dr Jude Hayward - 8 May)

Workstream Summaries

A. Informatics

Workstream Lead: Prof Philip Evans
Workshop Attendees: see Appendix 1

Several major areas emerged as barriers to current research:

1. **Inadequacy of family history recording**. This was a major issue that was inhibiting primary care genomics research. The ability to both record and then identify patients with a family history and hence identify patients by risk stratification through a positive family history was lacking. It was considered that family history recording was important on three counts:
    a. Establishing true genomic risk and enabling stratification for research.
    b. Establishing detailed phenotypic information for research purposes.
    c. Establishing possible familial inheritance and identifying individuals for cascade testing.

    Allied to family history was a need for better education (currently HEE driven) of GPs and other primary care professionals. There was a need for specific software to facilitate family history recording, potentially with template guidance. Despite the drive towards more detailed Whole Genome Sequencing (WGS), family history recording was still considered by the group to be a fundamental tool to facilitate genomic research in primary care.

2. **Recording of genomic abnormalities on primary care clinical systems**. It was considered that the move towards SNOMED coding with the ability to create new codes was an excellent opportunity to promote coding initiatives that would facilitate primary care research. Again, it was felt to be fundamental that the primary care GP record should reflect for future reference the results of any detailed laboratory genomic tests arising from CRN research. It was envisaged that these would range from a brief genomic report to susceptibility variants

included in a polygenic risk score, or indeed to the recording of WGS in an appropriate manner.

3. There was also felt to be a need for appropriate **recording of detailed phenotypic** traits and appropriate tests to exclude differential diagnoses. It was suggested that new SNOMED codes (for example for xanthomata) to assist diagnostic criteria for Familial Hypercholesterolaemia (FH) would need to be defined and agreed (currently the widely used Read code system in primary care contains several overlapping codes for diseases and patient characteristics). Patients with these possible genetic abnormalities could be then easily identified.
4. Similarly, it was considered moving forward as **pharmacogenomics** becomes more mainstream, that standard phenotypic definitions would need to be developed. These would then need to be recorded within the EHR in conjunction with decision support systems to flag up potential risks for future prescriptions and prevent adverse drug reactions. Aspirationally, it was also felt that GP electronic health records (EHR) (with consent) could be linked to the results of genomic databases, and integration into both clinical support tools and risk assessment tools based on genomic knowledge.

Recommendations

1. That the software system suppliers for GP clinical systems explore the potential for integration of dynamic family history recording tools into the electronic health record.
2. That family history software in clinical systems should include decision support modules to interpret family histories and advise on appropriate management.
3. That NHS Digital, along with key stakeholders, explores the ability of the new SNOMED codes to record in the electronic health record basic family history information as well as detailed genomic and phenotypic information.
4. That Genomics England and Health Education England, along with the RCGP and the CRN, consider updating existing and developing new educational resources for primary care staff, to enable optimal recording of family history.

For a more detailed discussion of the issues around family history recording please see Appendix 2

B. Operationalising genomics research in primary and community care

Workstream Lead: Dr Imran Rafi
Workshop Attendees: see Appendix 1

Several areas were discussed, mainly relating to the practical implementation of genomic research. Recent initiatives in genomics by NHS England, include a strategic approach to build a National Genomic Medicine Service, building on the NHS contribution to the 100,000 Genomes Project. (https://www.england.nhs.uk/genomics/nhs-genomic-med-service/)

Samples. There was discussion about the **cost of genomic testing**, which is reducing in scale with recent debate around cost-effectiveness in healthcare settings (Payne et al., 2018). Practices would need clear direction as to what type of specimen was needed, i.e. blood or saliva, how it was to be taken and how the specimens should be processed within what timeframe. This would need to be well-defined in the protocol and explained to the practice in the practice visit. It was considered that the BARCODE study of Prostate Cancer (PrCa) screening was an exemplar of an easy-to-run study in general practice.

Case Study 1

Case Study (from ICR website, https://www.icr.ac.uk/our-research/research-divisions/division-of-genetics-and-epidemiology/oncogenetics/research-projects/barcode-1)

The BARCODE 1 study has been developed to investigate the role of genetic profiling for targeting population screening. This study is a pilot of 300 men, with the view to continue to a future study of 5000 men.

The primary aim of this study is to determine the association of biopsy result with genetic risk score in men having targeted prostate screening based on single nucleotide polymorphism (SNP) risk profiling.

Men have been recruited from GP practices, a genetic profile of their prostate cancer risk performed (with the use of mouth swabs) and prostate biopsy offered to those in top 10% of the risk profile. The secondary aim of this study is to determine the incidence and aggressiveness of prostate cancer (PrCa) in men within the top 10% of the genetic score.

Additional blood, urine, saliva and tissue samples will be taken for research purposes in order to investigate new biomarkers in this population using biochemistry, proteomic, metabolomic and microarray approaches.

Samples will be collected from urine for further studies to correlate these with SNP profile, but biopsy decisions will not be made on these results. The tertiary aim of this study is to determine the association of biological sample biomarker profile with prostate biopsy result in men at genetically higher PrCa risk undergoing targeted PrCa screening.

GPs, practice managers, CRN facilitators and research staff from the Institute of Cancer Research have worked collaboratively and recruitment is now completed.

Secondly**, academic detailing**. This is the principle activity employed by pharmaceutical companies in visiting general practitioners and surgeries. It has been amended over the years to a system whereby trained individuals visit a practice in order to provide educational outreach and has been used in many Western healthcare systems (Van Hoof et al., 2015). It is the approach often taken by local CRNs when promoting a study direct to practices and is particularly pertinent in this genomic setting.

It should be acknowledged by all study teams that practices will need significant time for engagement to include specific briefing about the project, coupled with more generic genomic education. This need relates to the CRN clinical and non-clinical staff who will be visiting practices but also to the practice staff (including GPs themselves).

A basic level of **genomic literacy** will be needed in primary care to facilitate genomic studies by dealing with patient queries if GPs were either directly recruiting or feeding back results to patients. The FAMCAT study (Weng et al., 2015) aims to identify individuals at high risk of FH through electronic software integrated with the clinical EHR in primary care. This study has suggested that successful genomic testing in general practice needs to incorporate information for both clinical and non-clinical staff, e.g. a study protocol for management of genomic samples. This could easily be provided but allowance will need to be made in the **costing of studies** for this particular process to occur, possibly including any Excess Treatment Costs (ETCs).

Thirdly the **genetic testing registry** is currently being developed by Genomics England, as indicated earlier. At present this iterative process has not had significant input from either the NIHR CRN or the RCGP and it was thought that going forward this clinical database would be an important means of establishing a baseline for clinical genomic activity in primary care. Educational activities could then consolidate operational aspects and the database could provide opportunities for future research activities. Underlying the operational aspects of this workstream was a clear need for education.

Recommendations

1. That Genomics England consider how best to incorporate the views of primary care and primary care researchers into mainstream clinical genomic activity.
2. That the CRN work with primary care academics to further refine the costing process for genetic testing in the context of primary care genomic research.
3. That the CRN produces examples of good practice, probably via case studies, of how best to brief primary care teams and general practice staff about complex genomic studies, although this will vary considerably depending on the type of study.
4. That academic detailing for general practice led by the CRN should also include the procedure and timing of genomic testing in primary care.

5. That paperwork and electronic trails relating to genomic studies in primary care are concise and consider the range of healthcare professionals who might be involved.
6. That CRN staff facilitating genomic studies have a good understanding of the principles around genomics, including how informatics may help the study practices and practitioners to record genomic information in general practice.

C. Educational

Workstream Lead: Dr Jude Hayward
Workshop Attendees: see Appendix 1

Several aspects emerged:

1. A need for education was **cross-cutting** in the two other workstreams. Themes identified included: briefing research teams on a specific project coupled with generic genomic education, genomic literacy (including risk interpretation and study design limitations), recording of family history and appropriate use of coding. Two target groups were identified with overlapping and differing educational needs: those leading and conducting research studies, and NIHR and primary care staff involved in recruitment and delivery.
2. Development of educational material necessitates **identification of required knowledge and skills**, and **identification of existing resources**. A Delphi exercise conducted by HEE GEP (Genomics Education Programme) and led by Michelle Bishop and Jude Hayward established knowledge and skills required by GPs in the genomics era, and key areas were shared with the group: knowledge and communication skills around genomic concepts and genomic literacy, genetic conditions, clinical services and referral pathways, and an understanding of genomic tests and indications including an ability to take informed consent and an awareness of pharmacogenomics tests available.
3. Jude Hayward, on behalf of HEE GEP, has also produced an **audit of existing resources** covering general genetics and genomics for primary care. The CRN already provides GCP training for different audiences and has developed resources to support stratified medicine.
4. The RCGP (Clinical Champions Dr I Rafi and Dr J Hayward) and HEE in partnership are aiming to develop a **genomics toolkit**, and Kate Tatton-Brown is leading on development of targeted disease summaries which will form part of a ‘reactive’ suite of educational resources. It was suggested that these could contain a research section and resources specific to delivering genomics research in primary care.
5. Another key consideration was the **appropriate format of educational resources**; examples were discussed including information packs, delivery of face-to-face in-practice education, and integration into pre-existing frameworks such as nurse induction programmes. Development of **study-specific information packs** could potentially be helpful, but would need to be concise, and could signpost to or incorporate relevant pre-existing resources.

6. **Educational themes** emerged in addition to those identified through other workstreams: genetic and genomic literacy, clinical service configuration and pathways, implications of genomic testing for insurance, and consent. Those felt to be specific to delivering genomics research were **insurance implications** (relevant in application for ethical approval and in research delivery) and **consent** (taking consent and consent models).
7. **Consent**. There was a need for specific **consent training** both for CRN staff and for practice staff. It was suggested that this could be built into generic GCP training or developed into stand-alone GCP genomics training for primary care. This would need to be discussed and agreed with the CRN workforce team and would be an important initiative going forward.
8. There was also a recognition that the full range of healthcare professionals working within the CRN and Primary Care would need to be considered in developing educational material; pharmacists were given as an example.

Recommendations

1. That Genomics England and HEE include a research section in any genomics toolkit which will be available to GPs and primary care staff as part of their genomic educational resources.
2. That the CRN consider the need for development of training addressing specific needs, including insurance and consent training, or even a stand-alone GCP for genomics in primary care course to facilitate primary care genomic research.
3. That an appropriate framework is in place for supporting development of study-specific educational material. This will include promoting awareness of relevant educational needs, existing educational resources, appropriate formats, and knowledge and skills expected of primary care practitioners, in addition to an awareness of knowledge and skills which would not be expected of primary care practitioners. This will need to be collaborative between the CRN/RCGP/HEE/GE.

It is important to note that the views expressed in this document are those expressed by workstream delegates and not necessarily those of NIHR or the Department of Health. Many thanks to Dr Mariam Molokhia of King's College for her helpful internal peer-review of this document.

Appendix 1. Attendees and designations at each of the teleconferences

Appendix 2. Family history recording discussion paper – Professor Evans

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Appendix 1

RCGP / NIHR CRN Teleconference: Primary Care research in genomics

Date: Tuesday 26 June 2018

Informatics

Attendees

Helen Macdonald	CRN RDM Eastern
Helen Membrey	CRN RDM KSS
Imran Rafi	Chair of CIRC, RCGP/ RCGP Genomics Clinical champion/GP
Joanne Ashcroft	Assistant Cluster Lead Cluster C
Jozella Mearhart	KCL CRN Cluster Manager
Jude Hayward	GP/ Primary Care Adviser to HEE Genomics Programme/ RCGP Genomics Clinical Champion
Lisa Gibbons	GP and SW Peninsula CRN CRSL for Primary Care and National Primary Care IT Lead
Mariam Molokhia	GP and Clinical Reader in Epidemiology, King's College
Nadeem Qureshi	GP and Professor of General Practice University Nottingham
Philip Evans (Chair)	GP and National Clinical Specialty Lead for Primary Care and Cluster C Lead
Will Evans	GP Leeds, interest in genomics in Manchester and rare diseases

Apologies

Alison Marsh	
Mike Pringle	
Simon de Lusignan	
Vasa Curcin	

RCGP / NIHR CRN Teleconference: Primary Care research in genomics

Date: Tuesday 08 May 2018

Education and Operationalising

Attendees

Ana Guerra	Primary Care Link Manager, South London CRN, Division 5,
Andrea Haworth	Head of Clinical Services at *Congenica* – a genomics software company
Elizabeth Bancroft	Senior Research Nurse, Institute of Cancer Research
Eva McGrowder	Research Study Coordinator, Institute of Cancer Research
Greg Rubin	Prof of General Practice, Newcastle
Helen MacDonald	RDM, CRN Eastern
Imran Rafi	Chair of CIRC, RCGP/ RCGP Genomics Clinical champion
Joanne Ashcroft	Assistant Cluster Lead Cluster C
Jill Barlow	Primary Care Facilitator NW Coast CRN
Jane Beety	Head of Clinical Specialist Professional Engagement Programme CRN
John Castledine	Head of Learning Development and Design CRN
Jude Hayward	GP/ Primary Care Adviser to HEE Genomics Programme/RCGP Genomics Clinical Champion
Jo Mearhart	Specialty Cluster C Manager supporting primary care and genomics
Kate Maitland	CRN NW Coast – senior nurse
Kate Tatton-Brown	Consultant Clinical Geneticist and South London training programme
Michelle Bishop	Education lead for Genomics, HEE
Natalie Billington	Hub Manager CRN Kent Surrey Sussex
Nadeem Qureshi	GP and Professor of General Practice, Nottingham
Philip Evans (chair)	GP and CRN Primary Care National Specialty Lead / KCL Cluster Lead
Sarah Benafif	Clinical Research Fellow, ICR
Susan Rae	Lead research nurse in primary care for South London CRN
Theo Christie	CRN business development manager (Leeds)

Apologies

Andrea Beattie	Andrew McFarlane
Anne Oliver	Becky Dilley
Divya Chanda Manek	Fiona Walter
Hywel Bowen Perkins	John Spicer
Lisa Cheng	Michelle Ferris
Nicholas MacInnes	Ros Eeles
Shophia Kugan	Susan Willis
Wendy Godfrey	Zsofia Kote-Jarai

Unable to connect.

Liz Krymalowski	
Ali Marsh	

Appendix 2

The electronic recording of family history and genomic risk in general practice records

Background

General practice computing has been one of the great success stories in the NHS. Introduced in the early 1980s it has steadily spread so that today virtually all practices have sophisticated computerised records. General practice systems are far in advance of many computer systems used in Acute Trusts. However, the level and quality of family history recording in general practice records is poor (Dhiman et al., 2014), yet systematic family history recording can improve health outcomes (Qureshi et al., 2012).

This paper seeks to build on this asset to meet the need for much more information and better recording of family histories in the light of exciting new developments in genomics (Davies, 2017).

Family Practice

Worldwide, the main term for generalist doctors is 'family physician' and this captures the special framework in which doctors look after several members of a family simultaneously and often over several generations.

There are two scientific perspectives on family medicine. The first is the large number of diseases with a familial/genetic component which general practitioners see day-to-day. For example, 1 in 17 patients are estimated to have a so-called 'rare' disease (Hayward et al., 2017). This means that GPs are seeing patients who have a clinically important family history in a large number of day-to-day consultations.

The second scientific perspective is the research on family medicine which is long established. Professor Huygen, for example, in the Netherlands, as long ago as 1978, showed that illness in one member of a family group was significantly related to illness in other members and that the mother's health and pattern of behaviour was particularly influential. Huygen went so far as to conclude that in family practice "the family is the unit of care" (Huygen, 1990).

A family approach to medicine is one of the twenty core principles of general practice and one which gives general practitioners great interest (Pereira Gray, 2017) Facilitating the recording of family history in GP computing systems will have a bonus of making the day-to-day job more interesting.

Developments in genomics

Scientific advances in these areas have been among the most dramatic in medicine and have huge potential for the future of medical care. The NHS (Davies, 2017) has recently adopted this as a priority, both for clinical delivery and research, and this paper is written to underline ways in which general practice computing can be strengthened in response and hence facilitate this priority area.

General practice computing

General practice Electronic Health Records (EHRs) are comprehensive, cover a patient's demographic details and provide a long-term record of all consultations and hence automatically enable disease registers to be constructed. All prescriptions, both acute and repeat are recorded for analysis and there is now a steady flow of research publications making use of these data.

GPs already record family history as reported by patients but not in any systematised way. This often happens at registration. There is already a facility in some systems for checking registered patients who are living at a given address, but the striking gap is the difficulty GPs have in recording family trees over several generations. This is missing, even though family doctors in the NHS frequently have patients in three (sometimes four) generations, whom they know, simultaneously.

Pereira Gray (2017) in his Barbara Starfield memorial lecture noted that when he retired clinically from my practice, seven percent of all his personal list patients had four generations of the family registered simultaneously. This meant in practice that in every surgery session on average he would see a patient whom he could visualise as part of a four-generation family. This indicates that there is considerable scope for software which can help general practitioners see these relationships.

Main proposals:

1. **A need for better and systematic recording of family history for individual patients, e.g. premature coronary disease or breast cancer**

   Universally agreed Read (or SNOMED) codes and definitions of what constitutes a positive family history are needed, as are templates to facilitate accurate input. This will need technical input by the GP clinical systems suppliers and roll out, possibly with national financial incentivisation.

2. **A need for family history software to accurately record in a systematised manner the family history of patients and their families**

   Commercially available family history software is available, and the need is for this type of software to be incorporated into the main GP computing systems (EMIS and SystmOne) as soon as possible.

   Ideally such a system would also make it possible to link to the records of other registered family members or at least display any diseases or disorders with a strong genetic component.

3. **A need to integrate risk assessment tools incorporating emerging genomic information into clinical systems, e.g. Maturity Onset Diabetes of the Young (MODY) (Shields et al, 2012), or Familial Hypercholesterolaemia (Weng et al., 2015)**

The inclusion of genomic information into risk-profiling within the clinical systems will also need initial research and then implementation using innovative new clinical decision support software.

Longer-term planning

Looking to the future, it is necessary to anticipate an increase in genomic data becoming available for individual patients. Genomic information that could affect their health will need to be recorded in a systematic manner and be easily integrated with the GP record. Data protection issues and informed and full consent will be increasingly important.

Recommendation

That the NHS and the NIHR identify the systematic recording of family history and the ability to use family tree recording in general practice computer systems as a high priority. This will successfully underpin both research and service delivery.

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