# NIHR Think Research Rare Diseases Patient Day on 21 March 2018 Responses to questions raised on Glisser

Questions for the Consent panel are towards the end of the document

# **Presentation Title: What is the NIHR BioResource?**

Responses by Professor Patrick Chinnery

1. Can patient groups encourage researchers to use NIHR BioResource?

Yes, patient groups can encourage researchers to become involved, by championing their local NHS Trusts to become a recruiting site for the study. We currently have over 50 NHS Trusts recruiting to the NIHR BioResource -Rare Diseases study, but could potentially expand further. The patient groups also could help by making sure researchers/clinicians know about the BioResource, and are able to talk to patients about it.

1. Do you need large numbers of patients with certain diseases to make breakthroughs?

Not always, this depends on the condition. There have been breakthroughs in disease areas with only a few patients- but that is usually when the disease is severe, and monogenic (controlled by a single gene), as oppose to complex diseases involving several genes. However, when possible we like to recruit large number of participants, as if the cause is not a single gene disorder, it can be difficult to find a cause, and if you recruit patients with the same clinical features (phenotype), then you can compare their genetic makeup (genotype), as well as comparing it to affected and unaffected family members.

1. Has the moving of Rare Disease Translational Research into the BioResource diluted the work focussed on rare diseases or has it improved by opportunities for rare diseases?

No, there has been a natural decrease in activity as we had completed the recruitment and sequencing of 13,000 participants with Rare Diseases and their relatives; so, whilst the analyses and production of results has continued, the busy recruitment phase had finished. During this time, we have been able to incorporate the Rare Disease – Translational Research Collaboration into the BioResource, contact all the Rare Disease groups and ask them if they would like to recruit under the new framework.

There has been a lot of work regarding ethics and governance, and IT to get it to this stage, but we would have needed to do this anyway, as the paperwork we were using was five years old, and needed modernizing. We have everything in place to recruit from wide range of rare diseases, and believe the next five years will be very successful in terms of recruiting patients and driving research into Rare Diseases.

1. Will your treating healthcare providers have access to your sample results and be able to use this in enhancing your care?

The participant is able to choose if they would like pertinent findings feedback. Our current status is that if we find a pertinent genetic result regarding the reason the patient joined the study, and the participant has opted to have this feedback, then the result will go to the clinician, the clinician will ask the patient for a second sample to confirm the diagnosis in an accredited laboratory- and once this has been done, the clinician will give the diagnosis to the patients. This will likely drive their clinical care.

1. It's difficult for me to travel so how can I take part in the Bio resource if my local hospital isn't covered?

If you would like to take part in the BioResource, and are unable to get to a local centre, we could send a salvia kit to your house, and you could provide a spit sample. You would also need to complete a consent form, and a questionnaire on your health and lifestyle. This would be posted back to us in pre-paid packaging.

1. How do you ensure consent preferences follow samples if they are anonymised?

Samples are labelled with barcodes containing a unique identifier. This unique identifier is linked to the participant ID, which is linked to the participant’s name and personal details in the secure database. The database is kept up-to-date, and carefully stores this information, with regular backups of the servers happening, so that the data is maintained. We can interrogate the database for the sample identifiers at anytime.

1. Is it compulsory for researchers using bioresource data to participate in BioResource?

No, external researchers are also able to apply to use the BioResource. All researchers wishing to access data need to go on the NIHR BioResource website, request an application form, which is called a “Data Access Agreement”, complete and submit it. The Data Access Agreement application will be reviewed by the Committee, and checks made, such as the verifying the applicant, the organisitaion the applicant is working for, if they can safely use data, etc., the application will then be approved or rejected. If approved, the person will be given log-in details, and can log into the computer system that stores the genetic data, and access it. This type of data is view only, people are not permitted to take a copy, or remove the data, but they can use tools to do the analysis that they would like in the computer system.

1. Can patients with a diagnosis of a rare disease join the study?

Yes, if they would like to, they may join the BioResource. Our primary aim is to provide a facility for recall studies, so that we can recall our participants based on their clinical features or genetic make-up (or both), so if we know a patient has a diagnosis already, then they will still be a valuable member of the BioResource, and there may be subsequent research studies that interest them.

1. How do researchers access the DNA samples and/or genotypic/phenotypic data?

An application has to be completed for samples/genetic or phenotype data, this application form can be requested from the NIHR BioResource website; once completed it will be reviewed by the Steering Committee (comprised of the 13 local centres BioResource representatives, plus a patient representative, patient group representative, NOCRI, etc.). If an application is approved, then the NIHR BioResource team will work with the researcher to ensure their request can be delivered to them.

# **Presentation Title: Transition is about becoming a young adult not the medical condition**

Responses by Professor Allan Colver

1. How many young people were recruited to the programme and how were they selected?

374 young people. Over 14 and pre-transfer and without severe learning difficulties. Those approached with cerebral palsy were randomly selected form two regional populations cerebral palsy registers. Those approached with Diabetes were all young people at 5 diabetes clinics across England. Those with autism and mental problem – all young people attending 4 CAMHS services across England.

1. This is great but how can we convince adult services in my hospital to adopt this? Because it seems time consuming?

Our research stream around commissioning identified that adult commissioners do not commission for transition. So, this must change because then there becomes an obligation on adult services. Then of course one needs training and working together. Again, our research into this found that appointing a Transition Committee and a Transition co-coordinator across the Trust for all specialties and child and adult services really helps.

1. Sometimes in the early years we worry a lot about making sure that unique needs are met. How did the young people who volunteered felt about having different long-term conditions?

The UP group soon forgot about their underlying impairments when meeting with each other. Ground rules were set, enterprises were worked on jointly and of course the binding factor was the Research Programme not their treatment or individual problems.

1. Health self-efficacy: how do we promote it and when?

I think the ‘when’ is gradually from age 12 onwards.  
The ‘how’ is more difficult. We did not study this but it is one of our research recommendations. A Dutch group has worked a lot on it and found effective methods. However, other studies have developed approached which appear not to work.

1. Does peer-to-peer mentoring and support (young people with lived experience) play a role in improving the transfer and transition process?

We did not study this. There are some reports that it helps some young people but some young people actively avoid it.

1. Are you collaborating with other hospitals/doctors and sharing your findings to ensure that transition goes well?

We had a large dissemination conference in October 2017 for commissioners, NHS England, DH, Trust Chief Executives, and Royal Colleges, etc. Our research demonstrates the need for top down approaches as well as bottom up ones. We are now publishing key research papers to underpin our work. We are asked to talk at NHS Trusts around the country.  
The slides and videos of our talks at the October 2017 London meeting are on our website <http://research.ncl.ac.uk/transition/>

1. What age do you advocate for transfer?

I think it is unrealistic to expect that every young person can choose the age they want to transfer. There will be different approaches in different Trusts and specialties, some determined by legal issues, some by budgets. We argued strongly that if Developmentally Appropriate Healthcare (see my handout) is delivered by child and adult services, then it does not matter at what age transfer occurs; because developmentally appropriate care is offered for that young person in adult and child services

# **Presentation Title: Genetic Eye Disease - Light at the End of the Tunnel?**

Responses by Dr. Patrick Yu Wai Man

1. How are you going to get rid of geographical disparity in terms of testing 4 genetic eye disease?

We are fortunate in the UK that genetic testing is available within the NHS. However, there are wide variations between different centres depending on local expertise and the budget available. There are major changes coming around the corner in terms of how genetic services will be provided in the UK. The hope is that this restructuring programme together with rapid advances in next-generation sequencing technology will help bring cost down, providing a more comprehensive national coverage and allowing a genetic diagnosis to be reached faster than currently.

1. So, what does Brexit mean for international collaboration?

International collaboration will continue irrespective of Brexit. What we do not know (at least at this point in time) is whether UK researchers will still have access to EU research funding after the UK is due to leave the EU on the 29th of March 2019.

1. Is the current research based on preventing the condition from getting worse or focused more on finding an overall cure?

Each genetic eye disease is to some extent unique depending on the gene that is involved and the specific type of cells that are affected. Researchers are working on both strategies i.e. trying to develop treatment for a specific gene in a specific cell or aiming to develop a “generic” treatment that targets one pathway common to many genetic eye diseases. Time will tell and in the end, we might need more than one approach to stop someone’s vision from getting worse as disease can be complex.

1. What can a patient group do to facilitate the trials and move research forward?

Patient-led organisations play a crucial role, more so for rare diseases. They help generate greater awareness among the general public and they can help disseminate information to a wider audience, especially with the use of social medial tools. Patient groups can also be strong advocates, lobbying the Government to improve the healthcare resources available to patients and their families, and to invest more into research for rare diseases. It is also highly valuable to get the views of the patient community in the design of clinical trials and in prioritising areas of research.

1. Why is the treatment so expensive and will cost come down?

Developing a new treatment and taking it to market takes a long time and major capital investment. Drug companies need to recoup their cost to hopefully further invest into research. However, the high cost of new treatments is a major issue when faced with the reality of overstretched national health budgets. There is no easy answer and drug companies need to engage with the Government, NHS healthcare providers and patient-led organisations to reach a middle road that allows (faster) access to new treatments without punitive financial consequences.

# **Presentation Title: Creating the world's first children's centre for rare disease**

Responses by Dr. Larissa Kerecuk, Rare Disease Lead for BCH

1. What do you think is the most important element for paediatric Rare Disease care?

The most important element of caring for patients affected by Rare Diseases is holistic coordinated care. By the term holistic, I mean that health care professionals need to treat the affected child or young person in the setting of their family, carers, school and society. This starts by getting a diagnosis and thinking of how this impacts the rest of the family (genetic counselling but also a lot of guilt for parents); support and information about what the illness means and how to deal with different aspects of the condition. For a lot of rare diseases, the information is not accurate and pointing to the right sources is vital rather than the family using Dr Google which can be very frightening.

One of the most important aspects of holistic care is coordination of care: from multidisciplinary clinics, to having as many investigations done on as few trips to hospital as possible and for all the healthcare professionals to speak to each other and agree on a treatment plan rather than the family trying to coordinate everything and work out what should be done first and who needs to be consulted. Transition to adult care is a very important aspect of holistic care that should not be overlooked as this is a very stressful time for the patient and family.

Having a dedicated specialist nurse for the family is the approach we use at Birmingham Children’s Hospital thanks to the generosity of the Roald Dahl’s Marvellous Children’s Charity who fund Rare Disease Specialist Nurses to help the family navigate the health care system. The Roald Dahl Specialist Nurses also help with accessing the help that is available: from financial to psychological. Health care professionals need to remember that only 5% of those affected by rare diseases have any treatment so improving the quality of life involves addressing psychosocial issues that can make a big difference. Research needs to be part of holistic care as that gives hope not only for our patients now but also for those in other parts of the world and in the future too.

1. This is such essential work, if you didn't fundraise would this centre not have happened?

Sadly, without the generosity for the Birmingham Children’s Hospital Star Appeal, the rare disease centre would not be a possibility as there is no NHS funding for new buildings at present and the emphasis over the past 9 years has been to reduce spending. However, if we can show that the Rare Disease Centre makes a significant difference to patients and their families, then there may be enough evidence to develop other such centres.

1. Do you think the 100,000 Genome project will fully embed into the NHS?

Presumably the question is whether Personalised medicine will embed in the NHS as 100K Genome Project is due to finish recruiting in September this year. The uptake of the Project has been very variable across regions of the UK in the 13 different Genomic Medicine Centres. For instance, the West Midlands and London are top recruiters whereas other regions have a lower uptake. Equally, within regions there is variable uptake across the different hospitals. Generally, specialist hospitals have a higher uptake. In fact, Birmingham Children’s Hospital and Great Ormond Street Hospital for Children are the two single highest recruiting hospitals.

Therefore, the uptake of personalised medicine will mirror the update of the 100K Genome Project initially. We must remember that the UK are leading in terms of introducing genomics and personalised medicine into everyday practice and the legacy of the 100 k Genome Project means that the pathways and the systems will be in place to allow this revolution to continue. We are part of a very exciting new phase of medicine and the UK are leading on this.

1. Your model is great, but how do we export it for families who live very far away?

We have families who travel from all over the UK to attend our Highly Specialised Services and this is why it is so important for the care to be highly coordinated with as many of the health care professionals as possible seeing the patient and for as many of the investigations to be done when the family attends our hospital. Liaising with local hospitals and teams where the family lives is a very important aspect of care and communication is vital.

The role of the Specialist Nurses including the Roald Dahl Rare Disease Specialist Nurse in supporting the families wherever they live and involving all the agencies that can help to improve the quality of life as close as possible to where the family lives. In the new Rare Disease Centre, we have teleconference facilities and we are keen to use technology to reduce travelling. Involving the local paediatric team, community nurses and even the GP can also increase the knowledge about rare diseases for those supporting the family. Patient Support Groups are also able to help more locally.

1. What methods are used within the new rare disease centre to signpost rare disease patients and families to relevant support organisations?

Lots of our patients and families are already in contact with Patient Support Organisation as each of the teams dealing with rare conditions signpost families on reaching a diagnosis. In some teams, the specialist nurses ensure that this happens. In other teams, the consultant will do this. Personally, I always check if the family are already aware of the relevant patient support organisation. I find it is always best to check this as sometimes the obvious has not been done!

Each team that does clinics in the rare disease centre has been asked to invite the relevant patient support organisation to attend and be on hand to speak to families e.g. TSA (Tuberous Sclerosis Association), SWAN UK (Syndrome without a name), Wolfram UK, Bardet Biedl Association, Alstrom etc.

We also invite a whole range of organisations that can support the families to attend events at the hospital (e.g. Rare Disease Week), clinics and our Rare Disease Events E.g. Contact a Family, Carers Hub, Local Hospices, Together for Short Lives, Movement Centre, Citizen’s Advice Bureau etc. This helps everyone in a more generic way. I am the Chief Medical Advisor for Make a Wish UK and we refer lots of our brave patients and families for a special, once in a lifetime true wish which can help so much at very difficult times.

Our Roald Dahl Rare Disease Specialist Nurses have links to lots of patient support organisations and attend conferences and events to link up with many more such groups. We are very keen to collaborate with any organisations who can help our patients and their families.

Linking up with Patient Support Organisations is much easier in our day and age of social media – I link up with lots of rare disease organisations via Twitter (@BCH\_Rare).

1. After a child reaches adulthood will they need to reparticipate in research or will their data be carried over?

We always try to get assent from children for research projects. When they reach 16 years, they can consent to the studies themselves. If a young person was recruited to a study when they were a child, we will reconsent them if they have the capacity when they reach 16 years. For registry studies, we have to reconsent the young person by the time they reach 18 years otherwise, data cannot be collected after this age.

We have a lot of transition clinics when the adult hospital team and a team from our hospital are both present. It is a good opportunity to discuss all aspects of care including research so perfect time to re-consents for studies to continue after the age of 18 years.

1. Rare diseases cover diverse conditions, a big category. How can one multidisciplinary centre cover them all?

We have 35 different specialties at Birmingham Children’s Hospital and the rare disease centre holds several different clinics which each are staffed by the team looking after each rare disease or groups of rare diseases at different days and frequencies. For instance, Wolfram clinic is held 4 times per year and there is a specific team for this. Tuberous Sclerosis clinic is held once a month with a different team etc. Some teams have specialist nurses whilst other teams require input from the Roald Dahl Rare Disease Specialist Nurses.

The research team can recruit for a variety of research projects in the rare disease centre. For interventional studies, information can be given in the rare disease centre and then the families will attend the clinical research facility for the interventional aspect. Therefore, our approach is to tailor each clinic to the needs of the children affected by the particular conditions. There are lots of teams involved in the delivering care in the Rare Disease Centre.

**Poll results:**

Where would technology make a real difference within rare diseases?

* + By improving communication between the patient and care team - 2
  + By improving accurate diagnosis quicker, easier and more streamlined - 1
  + By supporting the seamless transition to adult services- 2
  + Be more science focused enabling new med tech to aid with treatment-0
  + Be more app and software focused to help with care management- 2

# **Presentation Title: Patients and Researchers collaborate to solve SCAD**

Responses by Dr. David Adlam (DA) & Rebecca Breslin (RB), BeatSCAD

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| 1. How do patients find out if they have this condition?   RB: SCAD is diagnosed by an interventional cardiologist during a coronary angiography which will usually be performed as a result of an acute event such as a heart attack or sudden cardiac arrest. |
| 1. Is it common for people as young as you to have this condition?   RB: The age range for known cases is currently 18 to 84 with the average age being around 42 so I was a bit younger than average at 34. |
| 1. What proportion of the research funds does BeatSCAD provide?   RB: I’m not sure of the percentage amount but fairly small so far. The majority of funding has been awarded by the NIHR and BHF.  DA: Yes, a small but critical portion. |
| 1. Is it a genetic condition?   RB: We don’t know yet. More research needed!  DA: So far it seems that for most patients the genetics are complex. We have identified a first common variant (a gene which contributes to risk but is also common in the population as a whole) and some rare variants (very uncommon genes which seem to be important in small numbers of SCAD-survivors) and are working on these at the moment. |
| 1. Becks, were you instantly diagnosed with SCAD?   RB: Pretty much. SCAD was suspected during the emergency coronary angiogram I had about 18 hours after my first heart attack symptoms at home. |
| 1. Do you have to take medication for SCAD?   RB: Research so far is showing that most SCAD patients will stabilise under a conservative treatment strategy (medications only) rather than the use of stents (which are the usual treatment for atherosclerotic heart attacks). The body will naturally try to heal the SCAD itself. Some SCAD cases are severe and require bypass surgery. I take three medications as a result of my SCAD and expect to be on them for life (unless research determines otherwise…). Not all SCAD patients stay on medication for life – it depends on the individual circumstances as to what may be beneficial. I have some permanent heart muscle damage so I take medications to lower my heart rate and keep my blood pressure low with the aim of reducing the overall workload of my heart. I also take aspirin as a blood thinner. |

# **Presentation Title: Gene therapy for inherited metabolic disorders**

Responses by Professor Paul Gissen

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| 1. Why is gene therapy so expensive?   It is expensive to develop a new therapy, do clinical trials and the company needs to recoup their investment. There are only few patients with rare diseases therefore per patient the treatment is expensive but compared with the common disease drugs on the large scale it is not more expensive. It may be cheaper than traditional therapies in the long run as the therapy may not need to be administered again. |
| 1. How common is liver disease?   Common liver diseases are very common: one of the commonest form of disease, similar to heart disease and cancer. Rare liver diseases are rare individually. Some are one in 10,000, others one in a million population. |
| 1. How long does trans genes take to become effective?   Could be as quick as 4-6 hours after administration. |
| 1. Will gene therapy reduce liver transplants?   Yes, it is possible for some of the conditions. |
| 1. Why not do genetic engineering like the Hunter Sangamo trial where the new gene replaces the broken gene in the genome?   Yes, it may be possible in the future. At the moment, it is not possible to do such replacement in every cell, which would be needed for some of the liver diseases. The technology is not at that level yet. Sangamo technology would be able to replace the faulty gene in less than 10% of liver cells. |
| 1. How many vectors are available? What is the difference between A AV and for example Lenti David?   The main viral vectors are Adeno Associated Vectors (AAV) and Lentiviral vectors (Lenti). There are many subtypes of AAV and some subtypes of Lenti.  There are some other vectors that are used in clinical trials such as adenoviral vectors. |

# **Training Sessions**

# **Data and Research**

Response by Neil Walker

1. How can patient groups collect data, build cohorts to help researchers?

**For Rare Disease patients:**

Currently the NIHR BioResource has asked clinicians in the BioResource centres across the country to nominate rare diseases they would be happy to champion; wehope that up to 100 rare diseases will be selected and cohorts of patients formed this way. We also encourage patient groups to put links to our website on their social media sites, so that other individuals with the same condition can be made aware of the BioResource, and have the opportunity to join.

**Common Disease Patients**

The NIHR BioResource also recruits participants with common diseases, such as Inflammatory Bowel Disease, patient groups and charities such as UK Crohn’s and Colitis are readily involved in helping spread the word about joining the BioResource. Patient groups are welcome to suggest to the BioResource what data is important to collect, and we are trialling different methods, such as the participant sending a quick text each month to notify us if they are in remission or experiencing a flare.

**Volunteer Cohorts**

Anyone over 16yrs old can volunteer to join the NIHR BioResource (children may join if they have a condition, such as asthma). Therefore, if you have a rare disease, but there is no cohort for you to join, you can volunteer and become involved this way. You will be asked a basic health and lifestyle questionnaire, and for access to your medical/health-related records, this will allow us to know vital information about participants for recall studies.

If you would like to join the NIHR BioResource, please contact: nbr@bioresource.nihr.ac.uk

# **Social Media**

Response by Emma Damian-Grint

1. How do you make everything shareable?

This is a reminder to make sure that your content works and can appear across the platforms you're using. For example, if you've uploaded a video to a closed Facebook group then make sure that your settings are set to 'public' when posting it so that someone is able to share that post directly from your group.

If you're using Instagram, make sure you have set it up so people are able to regram (repost) from your account. If you are sending jpegs or asking for people to add a photo etc, make sure that the jpegs do not exceed the maximum size for that platform. All this information on different platforms is just an internet search away! Consistent use of #'s and making sure you have the right settings on accounts makes the process of sharing your posts as easy as possible for the user and therefore helps with spreading your message.

# **Genomics Training Session**

Responses by Dr. Gemma Chandratillake and Karola Rehnstrom

1. How do you know what is the causative gene mutation in a patient with an unknown rare disease when you are looking at the whole genome?

We use several methods to point us to the right genetic change(s), for example:

1. We use phenotype data from the patient, i.e. their clinical features, to suggest genes that might be important. There is information that has been curated about the clinical features associated with changes in genes that are known to cause genetic disease, so we look to see if there are any genetic changes in the genes that have associated with the patient’s clinical features.
2. We use information about the inheritance pattern in the family. For example, if both parents are not affected by the disease, we can look and see if their child, who is affected, has any genetic changes that they don’t have. Such “de novo” changes could be the cause of the genetic condition.
3. We use several other types of evidence to help us distinguish genetic changes that could cause disease from those that are more likely to just be variation in the population. These are quite technical, but can be found here: https://www.acmg.net/docs/Standards\_Guidelines\_for\_the\_Interpretation\_of\_Sequence\_Variants.pdf
4. How do patients overcome barriers to getting a genetic diagnosis?

This is a really good question. It can be difficult for generalists (GPs, paediatricians) to recognise a rare genetic condition, and difficult for specialists to understand the whole picture rather than just their area of expertise. Clinical Genetics would often be the specialty most suited to put the pieces of the puzzle together and to order the most appropriate genetic test, so requesting a referral to a Clinical Genetics department would likely be a good approach. If a GP is unsure of the suitability of the referral, they can always call the Clinical Genetics department for advice.

1. Can all rare diseases be traced back to a genetic cause? I have been told that my disease stems from a genetic predisposition but is triggered by an environmental change. How might they know that?

About 80%, or four out of five, rare diseases are thought to be caused by genetic changes in a single gene. However, some rare diseases are “multifactorial” or “complex”, meaning that it is thought that they are caused by a combination of genetic and environmental influences. We can determine whether a disorder is likely due to a single genetic cause by looking at the things like the inheritance of the disorder in families, and twin studies. For example, if identical twins always both have the disorder, it is likely due to a single genetic cause. If identical twins can be discordant for the disorder, with one having it and the other not being affected, there must be something else apart from genetics influencing the disorder. There are other types of studies that look for genetic predispositions in *common* complex disorders. These are called “Genome-wide Association Studies”, and usually require very large patient groups to identify the genetic factors that predispose to these common conditions. It sounds like your disorder might be difficult to understand if it is rare but not caused by changes in a single gene.

1. If tissue is stored can children who have passed away be included and if so how do you get referred since you are no longer in the system?

In some cases, tissue from a deceased child could be included in the 100,000 Genomes project, if the parents of the deceased child would like for the family to take part and if the family’s clinician thinks the child had a condition which is eligible for the 100,000 Genomes project. The family would only be eligible to take part in the project if the information could benefit living relatives in some way. The best way to proceed is to discuss this with your doctor, or with your local Genomic Medicine Centre. Whether or not the family can be included in the project would also depend on the type and amount of tissue available for the deceased child. Again, your local Genomic Medicine Centre is able to discuss this with the laboratory where the tissue is held and explore if it could be used for the project.

1. If you have already been diagnosed with a condition via a microarray, can you still take part in the genomes project?

Only patients who do not have a genetic diagnosis are eligible to take part in the 100,000 Genomes project. It doesn’t matter if that diagnosis has been established by whole genome sequencing, a microarray or using a standard NHS genetic test for a single gene.

1. If you have been involved in a research project before, can you also be involved in the 100' 000 genomes?

In most cases the answer is yes, the only exception is if you have already taken part in another project where your whole genome has been sequenced – in that case the 100,000 Genomes Project wouldn’t add any further information. Also, you would not be able to take part in the project if the other research project had already established a genetic diagnosis for you, even if this was done using some other technology (for example microarrays, or sequencing of a smaller part of the genome, such as the exome (all genes) or a smaller number of genes)

1. Why do u need just 70K people to get 100k genomes?

The reason is that every cancer patient who takes part in the project, will contribute 2 genomes. One from the patient’s blood which is their “healthy” genome and the other genome is from the patient’s tumour. Comparing these two will help understand what genetic changes the tumour has undergone to develop from healthy tissue to become a cancer, and in some cases this could even help with picking a drug that works better for that specific tumour. It’s hoped that in the future there will be many more drugs which are targeted to tumours with specific genetic changes.

**Genomics Poll results:**

1. Have you ever taken part in a research project?

Yes – 23, No- 8

1. Have you ever been invited to take part in a research study but declined?

Yes, I have declined because of concerns around data sharing – 1

Yes, I have declined because of some other reason – 6

Yes, I have declined because of concerns around confidentiality - 3

1. If you were offered a genomic test, would you like to receive additional findings if they were as described previously - i.e. only for conditions where there is a treatment or screening option?

Yes – 27, No- 1, Not sure- 4

1. If you were offered a genomic test would you like to receive additional findings even if they were for conditions for which there was no intervention?

Yes – 7, No- 2, Not sure- 4

1. If you were offered a genomic test, would you like to receive additional findings if that had an impact on the resources available for diagnosing rare disease?

Yes, I would like as much information as possible about my family- 11

No, I would like the resources focused on rare disease research- 1

1. If you were taking part in a whole genome sequencing project, would you want to receive the raw data to use for further analysis?

Yes, I would be interested in using it to obtain further information - 5

No, I only want the interpretation from my doctor- 1

Not sure - 2

If given the chance I would ask for the data, not to use right now but just in case for the future-3

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# **Consent Panel**

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| 1. How do we ensure that language used for gaining consent is simple enough that the choices to participate are clear?   The Health Research Authority (HRA) has guidance on its website for researchers to encourage them to write patient information sheets and consent forms in a simple language – see the link to the HRA website below. <https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/>  In addition, Research Ethics committees review all the patient information sheets and consent forms to ensure that they are patient friendly. |
| 1. How can you find out who is the custodian of the data from a study that I’m taking part in?   The easiest way is to contact the study team directly and ask. Contact details for the lead investigator or the study manager will be provided on your participant information sheet.    If the study has ended or for some reason you cannot reach the study team, you can contact (a) the research compliance team of the University or other organisation that the study was linked to (this information will be in the participant information sheet), or (b) the research ethics committee listed on the patient information sheet. Contact details for the University/Research organisation or Research Ethics Committee can be found in an online search.    Generally, the data custodian for a University lead research study will be the lead investigator. For industry lead studies, they may have a data custodian for the overall organisation.  **Secondary response**  Normally the sponsor of the study will be the custodian of the data (NB the sponsor is necessarily the same as the funder). In some cases, only the investigator (researcher) will hold the identifiable data and they will pass anonymised data to the sponsor. The patient information sheet should spell out who your identifiable data will be shared with.   1. Will the changes in the new GDPR exempt patient groups? Will we need to re-consent past patients?   In its GDPR guidance, the Health Research Authority says: "in most cases *(of medical research)* you will NOT need to re-consent existing participants (or parents/ representatives for paediatric studies) in order to comply with GDPR. Unless you are making changes to your study processes or arrangements (e.g. changing what data you collect or how you will hold it), you will not need to re- consent existing participants’  I think by default the same applies to past patients. |
|  |
| 1. What are the key factors of consent and data handling that we need to consider when planning for a new study? Are there different rules for pilot studies?   Informed consent is one of the most important parts of ethical research. It ensures that participants are volunteering by free choice to take part in a study; which means that they need to know what they will be asked to do, what risks are involved for them, what the value of the study is and that they are always free to change their minds. Therefore, key factors include:  (1)    on-going informed consent – please remember, this is not a one time, paper signing process, but rather a continuous dialogue. For example, explaining the procedures for the current visit and asking if the participant would still like to take part.  (2)    Informing – it is important to remember that consent and informed consent are two different things. Informed consent has two parts: (a) informed, meaning that the participant understands what will happen, what the risks and benefits are and what will happen to information collected; and (b) consent – freely agreeing to take part. To inform someone a researcher needs to make sure that the written information is understandable to their population and covers all of the information of what will happen during the study. The risks and benefits also require careful thought and discussion within a team. Information sheets are always better if critiqued by the intended participant population. Also, double check that important points in your information sheet are listed on your consent form and that anything listed on the consent form was discussed in the information sheet.  The second part of informing is having a discussion with the potential participant and determining if they truly understand the information sheet. Please remember that the responsibility is on the study team to make sure potential participants understand the study and that they have capacity to consent for themselves.  (3)    Think about the future. If you would like to possibly contact the participants after the study is over, ask for their permission to do so. If you may want to use their data for something else in the future, it is critical to include re-contact permission, as the GDPR will require that you are specific in agreement of data use. D not be afraid to have optional items, such as this for people to consent to.  Rules, regulations and ethics are the same for pilot and full studies.    It may be helpful to think of the information sheet and consent as a contract or agreement between the participant and researcher.    For more specific information on designing information sheets and consent forms please see: <http://www.hra-decisiontools.org.uk/consent/>. Also, consider speaking with your colleagues, the research office, patients and others who are your study population and the HRA if in doubt.  **Secondary response**  When planning a new study the process for consent and data handling will need to be compliant with the new GDPR. Where consent is the legal basis for data processing, explicit consent will be required. This might mean that implied consent or opt out consent will not be sufficient. Public authorities may be able to use public interest as their legal basis for processing research data but they would still be expected to seek explicit consent for the intervention itself in research of an interventional nature. The rules for pilot studies are the same as for full studies. |
| 1. What are your views about children’s and young people’s consent to research participation, treatment and surgery?   The answer to this depends on what treatment or study we are discussing.    Laws for clinical trials specifically state that 16 years is the age of individual consent (vs child assent). No other adult can make a decision for a competent adult. If an adult lacks capacity, they require a consultee for research purposes.    Treatment and surgery are based on doctor/ surgeon judgement. In the absence of a guardian to consent or if a guardian refuses to consent for a life-saving treatment, legal action can be invoked for doctors/surgeons to make the choice on the patient’s behalf. As a child becomes older, as doctor or surgeon can also make a decision on whether or not he/she believes that the patient can make their own decision regarding treatment. This is known as Gillick competence and is often used in cases of reproductive care of those under 16 years of age.    For research outside of clinical trials, there are no rules/regulations about how old someone has to be to consent for themselves. If we think about why we have informed consent, it helps us to form views about how to manage informed consent with children. Consent is about respect for an individual’s autonomy or ability to freely decide what happens to them and with whom. As with paediatric care, all study procedures should be discussed with potential child participants, and at a minimum, children should be allowed to say that they do not want to participate and they should be respected.  Most ethics committees will also require age appropriate information sheets and assent forms, where a child has a place to make their ‘mark’ to show that they are willing to participate. As all individuals and study populations are different, it is the investigators’ responsibility to decide at what age children can comprehend basic information about a study and consider agreement, this is often around 5 years of age or so.  However, as children get older, we would encourage more thought into their ability to consent for themselves before the age of 16.  Additionally, we would suggest that informed consent for child participation in a study, be undertaken as a family discussion with parents/carers and children together, as the adult consents, but ultimately for something to happen to the child. |
| 1. What is dynamic consent?   Dynamic consent has been defined differently overtime. While in its purest form, it is simply how informed consent is meant to be carried out (i.e., continuous dialogues and reaffirmation of consent), it is currently defined as **“a personalised, digital interface to enable greater participant engagement in clinical and research activities over time”.**    Using digital tools to keep in contact with participants who engage regularly with online systems, is a great method for ensuring that they are kept up to date and can change their minds about the use of their data in the study over time. However, caution should be used not to rely on these tools only, as engagement is not always clear and conversations are one of the few ways we can determine understanding.  **Secondary response**  Dynamic consent is normally seen as a form of electronic online consent which can allow someone who has donated their tissue or data for research to tailor their consent permissions after they have donated and consented on an ongoing basis. Potentially they could opt in and out of various uses of their tissue/data and potentially also opt in and out of who their tissue/data is shared with.  The HRA has tested this concept with the public and whilst they initially quite liked the flexibility, most felt it was rather unrealistic to think that they would constantly change their own restrictions, especially if there was no prompting email or reason to check the site. The public overall preferred the notion of broad consent as a once and for all consent. |
| 1. With the advances in genomics, how can we ensure that people are given enough support to consider the implications of genetic testing?   This is a truly complicated ethical issue, as even those who have advanced degrees in this area cannot always understand the implications personal to them. Ethically, we ask researchers to make a decision to disclose or not disclose genetic information. We ask for this agreement up front with participants and inclusion of this in the PIS.  Researchers should not disclose genetic information that is not clinically accepted as a diagnostic indicator. There is a big difference between association and causation. In each study the ethical quandaries are different and each study is evaluated on its own. Researchers undertaking this type of work are encouraged to spend a significant amount of time discussing the ethics of informing and not informing before submitting an application to an ethics committee.  **Another response**  Genomics England have excellent examples of both consent forms and patient information sheets to be used when undertaking genetic testing for research. In addition, there needs to be a discussion of the implications, the type of feedback that individuals would like to receive and the opportunity to ask questions.  **Another response**  The 100,000 Genomes Project manages this by recruitment and return of results through clinical structures embedded within the NHS. One steam of the 100,000 Genomes Project, under Health Education England, is the Genomics Education Programme (see <https://www.genomicseducation.hee.nhs.uk> ) designed to upskill the healthcare workforce in genomics application, which includes upskilling in the ability and confidence for health care professionals to engage in genomic conversations. |
| 1. What kind of data do we need to be aware of for GDPR purposes? Are there some forms of data that don’t need to be GDPR compliant?   The definition of data covered by the GDPR is as follows: ‘personal data’ means any information relating to an identified or identifiable natural person (‘data subject’); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.  The HRA has issued [guidance on GDPR](https://www.hra.nhs.uk/about-us/news-updates/gdpr-guidance-researchers/) and research. |
| 1. Are there examples of compliant consent language that we can use?   Informed consent is less about compliance and more about respect of individuals.  For support on consent documents please see: [http://www.hra-decisiontools.org.uk/consent/.](http://www.hra-decisiontools.org.uk/consent/) However, before undertaking research with human participants, please review an online ethics training programme, such as TRREE <https://elearning.trree.org/>.  It would also be very helpful to review the Nuremberg Code <https://history.nih.gov/research/downloads/nuremberg.pdf> to understand informed consent and its value.    For compliance with GDPR, please review <https://www.eugdpr.org/> and <https://ico.org.uk/for-organisations/guide-to-the-general-data-protection-regulation-gdpr/>. There are no specific wording requirements, but rather general conduct. |
| 1. If I give consent for my child, will this be enduring or will he need to consent again when he transitions to adult services?   A child would be expected to consent for themselves when they reached the age of 16 years in a clinical trial and 18 years in other types of research. |
| 1. Do you (or any charities) have any good examples on how to explain GDPR whilst alongside conveying the benefits of sharing data (e.g. #datasaveslives)   GDPR and benefits of sharing data are not in conflict with one another. GDPR is not about limiting data sharing, it is about better data protection and more specific agreements between data custodians and those whose information is contained in the data.  **Another response**  Refer to ICO guidance – for research HRA is also releasing guidance. |
| 1. How do I know my personal data is safe/ protected when it is digitized? Do you have software to protect from hackers?   This depends on what data, who digitalised it, and where it is stored. The GDPR is an attempt to increase the protection of data, as this varies widely between organisations.  Data protection is not only a matter of technology (software and hardware) it is a matter of how an organisation functions, e.g., how diligent it is in monitoring hacking, how often it updates security, in what form data are stored, etc. For example, banking and medical data in electronic form have generally been held more securely than when in paper form.  One example, from the NHS, an incident occurred one day in a records room where a window was opened on a windy day and the paper records cascaded out of the records room on the 6thfloor across the entire hospital site. With some the current fully electronic medical records systems that are security compliant, there has not been an incident of hacking in any country across the 20 years that they have been active.  **Another response**  Different studies take different approaches, for the 100,000 Genomes Project, people interested in our approach can access an animation on our website (<https://www.genomicsengland.co.uk/taking-part/patient-information-sheets-and-consent-forms> ) or from this youtube channel (<https://www.youtube.com/channel/UCFVzGiIYp-nRxsOTjjNUqOg> ).  **Another response**  Also, with regard to the concerns about data security in questions 11 and 12, delegates may be interested to know about the pseudoanonymisation aspects of GDPR.  Basically, pseudoanonymisation is where you perform a step which masks the data, but which can be reversed.  So, you might use an encryption key which jumbles up the data and makes it unreadable but which can be reversed if you have the key.  GDPR suggests that pseudoanonymisation should be used to reduce the chances of data being accidentally shared.  If it is used, it is important the the encryption key is stored in a separate place to the data itself.  There are some big penalities on organisations, amounting to millions of Euros in the worst cases, if they fail to protect data properly, but if they use pseudoanonymisation with encryption then the penalties are reduced because the risks of data loss are greatly reduced.  For example, there have been a couple of well publicised incidents over the last couple of years where organisations have accidentally lost or published users account information (I recall one of the phone companies did this).  If they had encrypted the data, then even if it had fallen into the public domain it would not be possible for anyone else to read it without the key.  By encouraging organisations to do this, and potentially penalising them if they do not, then hopefully the GDPR will result in data becoming more secure.  When you are asked to consent to the use of your data, the organisation should give you some information about what steps they are taking to protect your data.  Consent from now on must be explicit, which means your data can only be used for a specific purpose to which you have consented. |
| 1. After the hacking of some NHS trusts last year what assurances can we take?   This is complicated, as the hacking in the NHS affected some trusts but not others. Currently, each NHS trust operates independently with respect to IT and security. This complicates matters. They have also committed different amounts of budget in this area.  NHS digital does review and spend money on this and there is a fairly robust process around data protection in the NHS, however, the culture of data security and data protection, including individuals’ behaviours have a huge impact on security and this is difficult to regulate.  If patients show that this is a priority by discussing it with NHS representatives and care providers in an NHS trust, this can help shift the culture in a positive way. Care providers and trusts tend to want to be responsive to their patients*.* |
| 1. What are the key factors of consent and data handling when planning a pilot study involving young children that considers the potential benefit of peer-led educational support?   The HRA has specific [guidance](http://www.hra-decisiontools.org.uk/consent/examples.html) on consent and patient information sheets for children and young people. Some of the key factors are that parents are expected to consent on behalf of a young child. A young child may be able to give assent but it may depend on their age and maturity. The age at which a child can consent for themselves in a clinical trial is 16 years.   1. What are the key factors of consent and data handling when planning a pilot study involving young children that considers the potential benefit of peer-led educational support?  |  | | --- | | I can’t really comment on the study objectives, but for all research projects involving young children, factors to consider might include: |  * Minimise the information collected to that which is essential to answer your research question. * Design your data collection tool such that personal data is not routinely collected.  Specifically, avoid using names, hospital numbers, addresses, email addresses on forms from which data will be entered into a database.  Instead assign a study number. * Consider only collecting month and year of birth, or even year alone, to give a sense of the age of subjects without using their full date of birth. * If you have to collect and retain personal data, ensure that it is encrypted and that the key which can reverse the encryption is stored separately from the data itself * For rare diseases, avoid collecting narrow geographical information in your database e.g. Town of residence * If you are planning a long-term project, be aware that patients who achieve the age of consent will need to consent for themselves at that age. * If you are collecting information from parents, e.g by interview or completion of questionnaire, even though the information relates to their children you may need to consider asking them to consent in their own right as well |
| 1. Consent seems to have become an industry in itself. Where are the vested interests in consent? |

Informed consent has been required since the Nuremberg Code and existed in a similar form as today 50 years prior. It has not really become an industry in itself. It may possibly appear this way as there is a lot of confusion around informed consent and ethics of human research in the UK. This is in part possibly due to a lack of training in this area at the advanced research degree level. Greater training is urgently needed.

Robust informed consent is part of the ethical review of any research study. The research ethics committees review information sheets and consent forms based on the interests of potential research participants only. However, the actual process of consenting participants is done within research teams, and their attitude toward the value of ethics and consent will matter. Education in this area is very important.