Genome sequencing: What do patients think?

Patient Charter
Genetic Alliance UK

Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 180 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine.

Genetic Alliance UK undertakes various projects and programmes that add evidence and knowledge to improve health service provision, research and support for families. These initiatives include:

- Rare Disease UK, a stakeholder coalition brought together to work with Government to develop the UK Strategy for Rare Diseases.
  www.raredisease.org.uk
- SWAN UK (syndromes without a name), a UK-wide network providing information and support to families of children without a diagnosis.
  www.undiagnosed.org.uk

Download a copy of this report here:
www.geneticalliance.org.uk/genomesequencingpatientcharter.htm

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The Genetic Alliance UK team
Executive summary

This Patient Charter makes 15 recommendations for consideration before genome sequencing becomes widely incorporated into NHS services. Recommendations are grouped under four broad themes, based on what patients told us was important to them.

Patients want the option to receive as much information about their health as possible from genome sequencing

- A flexible approach to the feedback of incidental findings to patients should be developed
- Further discussion and research on the risks and benefits of opportunistic screening needs to be had with patients, the wider public and healthcare professionals
- Obtaining a diagnosis should be the priority when genome sequencing is used in clinical practice and this should be reflected in the resources allocated to re-analysis and opportunistic screening
- Dynamic consent should be the standard model of consent when genome sequencing is used in clinical practice
- All findings from genome sequencing should be returned to patients by a trained professional, such as a genetic counsellor

Patients value genetic counselling and are keen for the support of genetic counsellors before and after genome sequencing

- All patients should be able to access a dedicated genetic counsellor before having their genome sequenced
- More support should be given to the training of genetic counsellors as the need for their services increases
- Statutory regulation of genetic counsellors needs to be established to ensure the services delivered to patients and families are appropriately assured
- Training for genetic counsellors should include education on genomic information
- All healthcare professionals should be trained to have a basic understanding and knowledge of genetics and genomics

Patients welcome the sharing of their genomic data for research purposes

- The NHS should take steps to enable the safe storage and sharing of patients’ genomic sequence data to maximise research opportunities
- Information provided to those having their genome sequenced should clearly describe the aims and objectives of all stakeholders that might access their data, and clearly communicate any implications for insurance
- Research to better understand newly identified conditions, investigate potential treatments and define prognoses should be incentivised
- Research studies and clinical care involving genome sequencing should be more closely integrated to reflect the patient experience

Patients think that the NHS needs to make more progress towards preparing for the integration of genome sequencing into clinical practice

- The NHS should engage with the patient community to develop accurate and comprehensive information on genome sequencing
Introduction

Genome sequencing offers great potential for the effective diagnosis and future treatment of many conditions. This, coupled with the fact that the speed and cost of sequencing a human genome have dropped dramatically, means that for the first time genomic medicine could become a reality for NHS healthcare.

In 2012, the Prime Minister committed to sequencing 100,000 genomes before the end of 2017, with the overall aim of the UK becoming the first country in the world to use genome sequencing in mainstream clinical practice.¹

As this initiative starts to take root within the NHS, healthcare policy and decision-makers will need to draw on the informed views of the patients and families who will be the end-beneficiaries of genomic sequencing technologies in order to make effective decisions around its use.

We hope that this Patient Charter will be used by policy and decision-makers to encourage more in-depth and creative public and patient involvement in health care decision-making.

Our approach

In order to establish what patients and families affected by diagnosed and undiagnosed genetic conditions thought about the use of genome sequencing within the NHS, Genetic Alliance UK carried out an online engagement project, ‘My Condition, My DNA’.

The study comprised four online sessions that included text, podcasts, videos and questions. Respondents were also encouraged to leave additional comments as free text. Participants were sent a session to complete each week over a period of one month. The sessions informed patients and their families about genome sequencing, as well as gathering their views on issues such as the disclosure of incidental findings, the possibility of opportunistic screening, the use of their data for research and informed consent. Participants were able to join in from the comfort of their own homes at a time convenient for them.

The project was approved by University College London’s Research Ethics Committee in March 2014, before we began to recruit participants to the study. Recruitment was solely through our patient group membership, and the membership of the Rare Disease UK and SWAN UK communities. Further information about Rare Disease UK and SWAN UK follows this introduction.

Who we worked with

144 people registered to participate in the project. Of this number, half of the participants had an undiagnosed genetic condition or had a child with an undiagnosed genetic condition. Half of the participants had a diagnosis for their genetic condition. 46 different conditions were reported and the most frequently cited were: BRCA1 and BRCA2 mutations, Fragile X Syndrome and Li-Fraumeni Syndrome.

Over 85% of participants were female and 89% of participants described their ethnic background as white British. Respondents ranged in age with the most frequently cited age ranging between 35 and 44 (37% of participants). Participants were recruited from all four nations of the UK.
99 people participated in session one. 73 people participated in session two. 60 people participated in session three and 56 people participated in session four.

When interpreting the findings of our work, it is valuable to note that the patients that we spoke to as part of our study are already living with a serious genetic condition, diagnosed or undiagnosed, or have a family member who is affected. Additionally, 83% of participants have already experienced genetic testing services through the NHS, whether for themselves or for their child.

Due to the rarity of their conditions, many of these patients will have in common that they have spent potentially long periods of time in search of a diagnosis and know well what it feels like to not have an explanation for their/their child’s condition. As such, these patients know the value that having a diagnosis can bring.

We know from the SWAN UK community in particular that families value a diagnosis even when this does not directly lead to new treatment options. For them a diagnosis could tell them what the future might hold: whether their child will walk or talk, or what their quality of life or life expectancy might be. Many families say that they can learn how to cope with not knowing but that their hope for a diagnosis never really goes away.

The experiences of these families have no doubt affected how they feel about genome sequencing and issues surrounding the disclosure of incidental findings and the use of personal genetic information for research.
Rare Disease UK (RDUK) is the national alliance for people with rare diseases and all who support them. Membership is open to all and includes patients and family members living with a rare disease, patient organisations, clinicians, researchers, academics and industry. RDUK provides a unified voice for the rare disease community, capturing the experiences of patients and families and raising the profile of rare diseases across the UK.

RDUK was established in November 2008, by Genetic Alliance UK, following the European Commission’s Communication on Rare Diseases: Europe’s Challenges. RDUK successfully campaigned for its adoption in June 2009. Since then, RDUK has worked to ensure that the UK’s health departments acted on their obligation to develop a UK Strategy for Rare Diseases, and worked to engage with the rare disease community to shape its content. Since the publication of the UK Strategy for Rare Disease by the Department of Health in November 2013, RDUK has focused on ensuring that the implementation of the UK Strategy is effective and accountable.

www.raredisease.org.uk

SWAN UK (syndromes without a name) is an initiative run by Genetic Alliance UK offering support and information to families of children with undiagnosed genetic conditions.

Not having a diagnosis can be very isolating for families and SWAN UK aims to combat this by providing online peer-to-peer support, as well as providing and signposting to useful information. SWAN UK is also raising public and professional awareness of undiagnosed genetic conditions and the unique challenges faced by affected families.

SWAN UK launched in May 2011 thanks to a five-year grant from the National Lottery through the Big Lottery Fund, and in 2014 it received a second grant from the National Lottery through the Big Lottery Fund to establish the first local SWAN UK support networks in England. Since launching, SWAN UK has been approached by over 1000 families and was shortlisted in the 2013 National Lottery Awards in the 'best health project' category.

www.undiagnosed.org.uk
Case study

Sarah and Nigel have four children: Ben (18), Immy (17) and the twins, Joel and Toby, who are both five-years-old. Joel had a previously undiagnosed genetic condition but after being part of the DDD study for two and a half years, he now has a long-awaited diagnosis of Bardet-Biedl syndrome.

We didn’t realise that there was anything majorly wrong with Joel until he was about a year old. When he was six-months-old we started to think that there were a few issues with his physical development and he had some issues with hypotonia and hypermobility. He was seen by a physiotherapist and it was only after about a year that the physiotherapist said that they’d like to refer him for a general assessment by a paediatrician.

When the time came for us to go and see the paediatrician, I’d already worked out that Joel was on the autism spectrum by the way he reacted to certain situations and noises. We had an incredibly long appointment with the paediatrician and at the end of it she asked us what we thought was wrong with Joel. I said that I thought he was on the autism spectrum and she agreed but she also thought that he had a genetic syndrome. That absolutely threw us – we were not expecting that at all. So from that point onwards, we knew that Joel had some sort of underlying syndrome but the regular blood tests came back fine, the microarray and whatever else they did were absolutely fine so then we were referred to the geneticist.

Just before we saw the geneticist we got Joel’s initial blood tests back that said there were no chromosomal abnormalities so we thought, “great, the geneticist is going to see us and because the blood tests are fine, she’s going to discharge us because there’s nothing wrong.” But we went to see her and she said that because Joel’s got dysmorphic features that meant that he definitely had some underlying genetic syndrome. She said it was going to be like looking for a needle in a haystack because his features and difficulties don’t point in any particular direction so it would be difficult to find out what was wrong with Joel.

The geneticist did more blood tests, some more microarrays and some urine tests as she said she wanted to rule out a few things. She said that Joel would always remain under the genetics team even if they didn’t find out what the exact cause of Joel’s condition. We went away and all the tests that she had run came back normal. In the mean time I searched on Google and found SWAN UK. I discovered that there was a whole load of children out there with undiagnosed genetic syndromes, which reassured us that we were not alone. It was just really nice to be part of a community of people in a similar position. In amongst my reading and Google searches and being in touch with various people through SWAN UK I found out about the DDD study.

At the next appointment with the geneticist – which was an ordeal because Joel used to find appointments incredibly distressing – she mentioned what we could start doing next. She’d run all of the tests and she said that there were no symptoms pointing in any particular direction so she mentioned DDD. The nurse that was there with her took our sample there and then. Joel was crying so much because he hated being there but that meant that he produced lots of saliva really quickly, which was good! That was in November 2011.

I felt relieved that we were on the one thing that could potentially give us an answer but we knew we were in for a long wait. At that stage there was talk of it taking a year or 18
months for results, but actually it’s been a bit longer. At the time I did think to myself, “if this
doesn’t give us an answer then what will?” It was like an all or nothing situation for us.

People would ask about Joel and we’d say that he had an undiagnosed genetic syndrome but
because it didn’t have a name and it hadn’t been identified, people either used to think that
we were making it up for the sake of it or that he didn’t really have any problems. I used to
hate getting into that conversation with people because there was never an easy answer. Joel
is a twin, which also made his difficulties more obvious. Toby was hitting his milestones when
he should and because Joel wasn’t, it’s always felt like they’ve never really been twins and a
lot of people don’t realise that they are. Physically, Joel is a lot smaller than Toby and he is
behind in everything so people never realise that they’re twins because they’re at different
stages and they also go to separate schools. We’ve never had to buy two lots of clothes
because Joel is in Toby’s hand-me-downs, which is a bit sad.

The only contact that we had with the DDD study was through our regional genetics service so
it was just a case of waiting to hear something from them. We didn’t hear anything for ages
but we finally got a letter in April 2014. When it arrived I felt sick. I opened it and before
reading it I thought, “crumbs, this is it.” It was the letter that we’d been longing for and
dreading all in one go and I literally did feel sick because suddenly they’ve found something.
We had to wait to get an appointment with our geneticist though and that didn’t come until
the end of May.

When we arrived at the hospital our geneticist told us that the results were quite a surprise to
her. She asked whether we’d heard of Bardet-Biedl syndrome. Of course we said, “no”. She
explained that a mutation had been found on one of Joel’s genes, known as BBS9. She said
that it was a recessive condition and that Joel had inherited the faulty gene from both of us.

Now that we have a diagnosis, Joel is seen under a specialist team at Great Ormond Street
Hospital (GOSH) and he has an annual appointment where he goes and sees all sorts of
clinicians. He had his first appointment in September and we went and met the geneticist, the
ophthalmologist, clinical psychologist, dietician, endocrinologist and a whole range of other
people. One good thing was that Joel had some very specific ophthalmic tests and he’d have
never had those if he didn’t have a diagnosis from the DDD study and it’s likely that no one
would ever have realised that he needed them.

Having a diagnosis has always been important for us to be able to know what’s causing
Joel’s difficulties and why. It’s nice to literally have a name to be able to put in the box when
I’m filling in forms. Previously, I’d have to write down that Joel had autism as well as some
undiagnosed genetic syndrome but now I just write that he has autism and Bardet-Biedl
Syndrome. We’ve joined the Bardet-Biedl Society and they’ve been really supportive and
we’ve definitely had access to services that we wouldn’t have previously had access to. We
always imagined that getting a diagnosis would be the final piece of the puzzle and the end
of the journey, but it now feels as if we are at the very beginning of a new journey!

Many of the SWAN UK community are taking part in the DDD study, which they hope will be able to
give them a diagnosis. The pilot DDD study has allowed almost a third of families to get a diagnosis
and 12 new developmental disorder genes have been discovered. As the number of samples to be
analysed increases, the project team hopes that it will be able to distinguish further causes of
developmental delay and provide more families with a diagnosis.
Background to additional findings that could arise from genomic sequencing

At the moment most genetic tests look at just one or two genes, or a small panel of genes, in order to answer a specific clinical question. The test may be used to see whether an individual has inherited a known genetic condition or to try to get a genetic diagnosis that explains a patient's symptoms. In these circumstances, the genetic test is most likely to give a 'yes' or 'no' answer: whether the individual has inherited the said condition, or whether the test can confirm a suspected diagnosis. Genome sequencing allows us to examine more of our genes at the same time. It is only when we examine more of our genes in this way that we can start to ask more general questions and more questions at the same time. A consequence of this approach is that individuals may get answers that they weren't expecting or answers to questions that they had not intended to ask.

This more open questioning of the genome could enable patients to receive a diagnosis for their condition when previously it may never have been possible to establish a cause. However, in looking for a diagnosis, it is possible to discover additional information about an individual's health. For example, an individual could carry a genetic alteration that is associated with an increased risk of breast cancer, heart disease or dementia. It could also reveal that an individual is a carrier of a rare genetic condition, such as cystic fibrosis or sickle cell anaemia. Additional information like this could come as a shock or could be expected depending on whether the patient is aware of having a family history of that specific condition.

There are three ways that an individual may find out this 'extra' information from their genome while it is being analysed in the search for a diagnosis:

The first is if it is actively looked for by a geneticist who would use the opportunity of analysing the genome for diagnostic purposes to find out more information about a patient's health. Such findings are known as 'opportunistic findings'.

The second is if by looking for a diagnosis, something else is accidentally found out by the person analysing the genome. For example, it may be that near to the section of DNA that is being analysed to try and determine a diagnosis, a geneticist notices a genetic alteration that they know corresponds with another, distinct condition. This could be described as being similar to a scenario in which a doctor is examining a suspected breast cancer tumour but in doing so notices a skin cancer lesion. Such findings are called 'incidental findings'.

The final way is when looking for a genetic change in a gene that could establish a diagnosis for a condition, the same genetic alteration also indicates that a patient is affected by, or has an increased risk of developing, a separate condition. For example, alterations in a number of genes have been linked to causing developmental delay but the same genes have also been linked to some cancers and neurological conditions. It may be that the specific alteration identified by geneticists cannot explain the individual's condition but may still say something important about their current or future health. Such findings are known as 'co-incidental findings'.

This terminology should be noted when comparing the findings and recommendations of this report with others that may use alternative language. Hereafter, the term 'incidental finding' shall be used in this report to also encompass 'co-incidental findings'.
The current approach to the management of additional findings

Unintentionally finding something out about an individual’s health when looking into a separate condition – an ‘incidental’ finding – is not unique to genome sequencing. As described in the box above, this could include identifying a skin cancer lesion when examining a patient for a suspected breast cancer lump. Other examples include spotting something unusual in a patient’s blood test results that requires further clinical follow-up or diagnosing a brain aneurysm following a routine MRI scan after a head injury. Despite this, there has been much debate about incidental findings arising from genome sequencing and whether they are appropriate to be disclosed to patients.3,4,5

The current stance of the medical profession on the sharing of incidental findings with patients is guided by a report from the Joint Committee on Genomics in Medicine (formerly the Joint Committee on Medical Genetics), which brings together the British Society for Genetic Medicine, the Royal College of Physicians and the Royal College of Pathologists. This states that where the likelihood of something unexpected about an individual’s health being accidentally revealed is high, such as through genome sequencing, that the “possibility should be included in the initial consent process.” It also states that “more research is needed as to how this can best be addressed in both consent and disclosure practices, as well as how to address the implications for other family members.”6

As genome sequencing becomes a more routine aspect of clinical care, more specific guidelines on when it is appropriate to release certain types of information to patients should be made available in order to provide clarity both to healthcare professionals and patients and families.

There are a variety of findings that could arise from genome sequencing in addition to the ‘pertinent finding’, the reason why the individual was having their genome sequenced. This includes findings of unknown significance - those genetic alterations where we currently do not know how they might affect an individual or their health – as well as a wide range of findings that could be considered ‘clinically significant’. Some examples include the diagnosis of a condition that may or may not be treatable, identifying a genetic alteration associated with an increased risk of developing a condition in the future, or discovering that an individual is a carrier of a condition that does not affect their health but may affect their future reproductive choices. There has been substantial debate around whether the approach taken by clinicians on whether these findings should or should not be fed back to patients should be determined by the type of ‘clinically significant’ finding.

It has been suggested by some stakeholders that one way to limit the complex decisions that clinicians will have to make about whether to return incidental and co-incidental findings to patients is by reducing the number that are produced. One suggestion from recent work by the PHG Foundation proposes that one way to do this would be to limit the amount of the sequenced genome that is analysed, focusing only on specific genes of interest or modifying the process of bioinformatic analyses.7 During our study, we did not specifically ask patients whether they would want such approaches to be taken to reduce the number of incidental and/or co-incidental findings that could be revealed by genome sequencing. Further research and discussion with the patient community on these proposals would be valuable.

The patient view on additional findings

Through our ‘My Condition, My DNA’ project, Genetic Alliance UK asked patients what they thought about the different types of incidental findings that could be revealed by genome sequencing and how that might affect their desire to know this information.

Our study revealed that the majority of patients want to know anything that a geneticist might accidentally discovers during the analysis of their genome, regardless of the seriousness of the condition the finding relates to, or whether it is clinically actionable. Where there is variation between the preferences of individuals, this relates to whether or not the condition can be treated or prevented. Further discussion with a selection of patients also highlighted that some individuals would
like to receive information about genetic variants even when the scientific significance remains unknown.

Imagine yourself in the following situations. Please select the response that best describes how you would feel.

If a finding shows that I have a life-threatening condition that could be prevented and/or treated then...

If a finding shows that I have a life-threatening condition that could not be prevented and/or treated then...

If a finding shows that I have a condition (non life-threatening) that could be prevented and/or treated then...

If a finding shows that I have a condition (non life-threatening) that could not be prevented and/or treated then...

- ...I definitely would not want to know
- ...I don’t think that I would want to know
- ...I’m not sure if I would want to know
- ...I think that I would want to know
- ...I definitely would want to know

Previous thinking on the feedback of incidental findings has raised the concern that telling individuals about findings that are not clinically actionable and/or are not preventable could have a more negative impact on the individual than if they were not told. As a result, many medical professionals tend to be against returning such information to patients if it falls outside of the clinical question that genome sequencing was being used to answer, or if it does not translate into an immediate need for clinical action.

The outcome of our study presents a strong challenge to this established position. As explained in our

“If a life-threatening condition with no possible prevention was found I would not want to know as it would impact me negatively and overshadow my whole life making me anxious.”
introduction however, many of the patients who participated in this study have already experienced genetic testing in the context of the NHS and are aware of the limitations that genetic information can provide. It is important to recognise that this group of individual patients and families are, on average, more comfortable with and knowledgeable about the type of information that genome sequencing could provide, and therefore more keen to be told about, and more able to understand, incidental findings. However, if genome sequencing is to be used as part of NHS clinical practice, one of the primary uses, at least in the first instance, it is likely to be in diagnostics.

The patients and families who are most likely to be using this technology are those that we have engaged with: individuals or families with children that have undiagnosed conditions or have experienced being undiagnosed for at least some time. The views expressed in this study are likely to be representative of the voice of the community most likely to be have genome sequencing as part of their NHS care in the most immediate term.

Imagine yourself in the following situations.
Please select the response that best describes how you would feel.

If a finding shows that I may **develop a condition later in life** then...

If a finding shows that I am a **carrier of a condition** that I may pass on to my children then...

- ...I definitely would not want to know
- ...I don’t think that I would want to know
- ...I’m not sure if I would want to know
- ...I think that I would want to know
- ...I definitely would want to know
- ...it depends on whether or not it’s treatable

There is a need for further dialogue between healthcare professionals and patients to fine-tune how to proceed with the return of incidental findings once genome sequencing becomes a more routine aspect of clinical care. We have found that patients would like the option to receive the incidental findings that could be revealed through genome sequencing.

**Recommendation:** A flexible approach to the feedback of incidental findings to patients should be developed
Opportunistic screening

At least in the immediate future, the application of genome sequencing is likely to be used exclusively as an additional tool available to clinicians in order to answer discrete clinical questions, often in the search for a diagnosis. In much the same way as a doctor would look at a urine sample specifically to determine the presence of bacterial infection, a clinician will examine a patient’s genome in search only of those genetic changes that may be responsible for their condition. It is possible however, to find out many things about an individual’s health from similar routine tests. A blood sample could be tested for signs of cancer, for problems with the immune system or for abnormal hormone levels, for example. Similarly, when a patient’s genome is sequenced in an attempt to determine a diagnosis, there are additional questions that could be asked of the genome, which could reveal further information about an individual’s health. This is often described as ‘opportunistic screening’.

Opportunistic screening of the genome is not currently offered as part of NHS care. A similar approach is used in the NHS in primary care though, as identified high risk populations are offered testing for conditions based on broad criteria, such as in high HIV prevalence areas.\(^8\)

The 100,000 Genomes Project, which began recruiting participants in February 2015, is the first example of whole genome sequencing being incorporated into routine healthcare provision on the NHS. Part pilot study, part research, the project will be collecting the genetic information of around 75,000 individuals with cancer, rare disease and infectious diseases as the precursor to much wider ambitions to make genome sequencing a standard option for healthcare professionals to use as part of their clinical armoury. The way that the 100,000 Genomes Project has been set up means that individuals are being asked whether they would like to find out additional information about their health if it relates to a condition that is serious and clinically actionable on the NHS. Please see the box on page 18 for further details.

Patient view on opportunistic screening

We asked patients what they thought about opportunistic screening of the genome if it were to be offered to them as part of NHS care. Under the same scenarios that were given for the return of incidental findings, patients told us that they would want the person analysing their genome to purposefully look for genetic alterations that have been linked to conditions that are unrelated to the original diagnostic aim. The seriousness of the condition being searched for as well as clinical outcome, did not greatly affect patients’ views on this issue.

Please select the responses that best describe how you would feel.
I’d like a geneticist to purposefully examine my genome to look to see if they could find out if...

- ...I had a life-threatening condition that could be prevented
- ...I had a condition (not life-threatening) that could be prevented
- ...I was a carrier of a condition that may affect my children
- ...I had a condition that I may develop later in life
- ...I had a condition (not life-threatening) that could not be prevented
- ...I had a life-threatening condition that could not be prevented
Our findings are consistent with those gathered through other independent studies which found that many patients want to know additional information about their health that could be uncovered by genome sequencing, irrespective of the severity of the condition or how treatable it is.9,10

If opportunistic screening were to become a routine part of genomic sequencing in clinical care, the resource demand would be significant. The amount of genomic information that would have to be analysed, interpreted and returned to patients would be greater than if the technology was used to report back only those findings that were revealed during its use as a diagnostic tool. Opportunistic screening would also likely mean that more individuals would discover health issues that would require treatment or surveillance as part of NHS provision. Again, this could significantly impact NHS resources by increasing the number of patients who may require treatment or services. Alternatively, it could be argued that by enabling earlier intervention, the pressure on the NHS could be reduced. It is widely recognised, for example, that prompt diagnosis and intervention in those with the early stages of cancer and cardiovascular disease can significantly improve clinical outcomes for those individuals.

There may be a balance between such scenarios that could be met by considering the risks and benefits of opportunistically scrutinising the genome for particular conditions or risk variants. This could be thought of as analogous to other population screening programmes, such as cervical smear tests or newborn screening, where it is found that the benefits to patients from these programmes outweighs the resources required to implement them. Indeed, in its most recent review, the UK National Screening Committee asked whether population wide screening to look for specific genetic variants or risk factors was something that they should start to consider in their programme.11

**Recommendation:** Further discussion and research on the risks and benefits of opportunistic screening needs to be had with patients, the wider public and healthcare professionals.

**Storage and reanalysis of genomic information**

An individual’s genome sequence does not change over time. This means that rather than presenting a single opportunity in time to determine an individual’s current or future health state, there is the potential for genome sequences to be stored and interrogated at later stages in an individual’s life. One application of this could be that the genome sequence is used to answer different questions, as an individual gets older. For example, a 20-year-old patient may be less interested in an adult-onset condition than an individual in their fifties. Another application is that it would be possible to re-examine an individual’s genome sequence in light of new scientific discoveries without needing to repeat the sequencing. This could mean that a genome analysed in five years time could reveal more information about an individual’s current or future health than if the genome was sequenced and analysed today.

This latter application is of particular interest to the patients that participated in our study as their main interest in this technology in the first instance is in its ability to provide a timely and accurate diagnosis for their own condition or their child’s condition. If, after the first analysis of the genome no genetic variant is identified that could offer an explanation for their or their child’s condition, the possibility that the sequence could be stored and routinely reanalysed in light of new scientific discoveries was overwhelmingly supported. This further emphasises the value that this patient community put on achieving a diagnosis for their condition or the condition affecting their child.

As discussed above, there are potential resource limitations in the NHS, which may affect the ability to store and re-examine the genome sequence of every individual who was having their genome sequenced for diagnostic purposes. In light of the responses we obtained from our study and from what we know of our patient community, it is clear that at least one priority for the allocation of such resources should be to ensure that as many patients as possible obtain a diagnosis for themselves or their loved one. In order to achieve this, it may be necessary for the NHS to apportion less resource to opportunistically screening the genome, for example.
If you had your genome sequenced, would you like your sequenced genome to be kept and continually re-analysed in future in search for a diagnosis?

- Yes
- I’m unsure
- No

To explore further with patients what they think about the potential trade-off needed in order to focus on obtaining diagnoses from genome sequencing in the NHS at the expense of exploiting the potential uses of opportunistic screening, we approached our SWAN UK community. When we asked them what they thought the NHS should focus on in the context of finite resources they said that getting a diagnosis was the priority for them and that they would value this over finding out additional information about their own, or their child’s health.

“Our lives are put on hold until we get a diagnosis with regards to having more children (and time is running out!) also we would like to be able to prepare our daughter with regards to having her own children in the future. Diagnosis should definitely be the priority above all else.”

“Recommendation: Obtaining a diagnosis should be the priority when genome sequencing is used in clinical practice and this should be reflected in the resources allocated to re-analysis and opportunistic screening.

Consent for clinical use of genome sequencing

Information about our current and future health is very personal and it should be expected that there will be variation between individuals. It is also possible than an individual’s preferences may change over time. It may be that since an individual first gave their consent, their personal circumstances or their health status may have changed. An individual may have recently discovered that they have a family history of a particular condition, for example, and no longer want to know whether they have inherited it or not.

For many of the questions we asked in our study, the vast majority of participants responded in the same way: they were keen to hear back about incidental regardless of the nature of such findings,
were interested in the potential of opportunistic screening and supported the storage and re-analysis of genome sequencing in order to keep searching for a diagnosis.

Despite this general consensus however, there were some individuals whose attitudes differed from the majority. This emphasises that a ‘one-size-fits-all’ approach to consent is not appropriate for governing the terms within which an individual consents to the use of genome sequencing, even within a population where the vast majority of individuals would want as much information as possible.

Models of consent: an example from the 100,000 Genomes Project

In addition to results regarding a patient’s ‘main condition’ (the rare disease or cancer which led them to participate in the Project), participants in the 100,000 Genomes Project can ask to receive ‘additional findings’, fed back to them via their medical team. This is information about a specific list of ‘serious but actionable’ conditions, usually unrelated to the main condition.

These conditions can either be prevented or their impact reduced through interventions available on the NHS. Participants choose whether to receive results relating the whole list, or none at all. The list will be reviewed over time, with conditions being added or removed to the list based on scientific advice. The consent given is to receive additional findings from the list, in the understanding that this list is maintained according to specific criteria. Consent is therefore not given to a fixed list of conditions. If new conditions are added to the list, they will automatically receive feedback on these too, or the opposite where existing conditions on the list are removed.

Dynamic consent is a model of consent that makes it possible for individuals to continually adjust and re-adjust their preferences as to which information they receive about their genome. This process could either work by allowing the individual to reconsider their preferences whenever they choose or could be solicited by the NHS after certain periods of time, or a combination of the two.

Would you want to be able to update your consent regarding genome sequencing at any time?
In other words, should dynamic consent be in place?

When we asked them, patients indicated that dynamic consent would be the most appropriate model for consent in the context of genome sequencing in the NHS for two reasons. Firstly, the majority of respondents thought it was important for patients to be able to change their mind about what information they want to receive from genome sequencing. Secondly, a significant proportion of respondents felt that the individual should be able to determine what results they are given following the analysis of their genome. Only a much smaller proportion of respondents were happy with the solution that the NHS only feedback information to patients based on standardised criteria.
The value of dynamic consent may be most clearly demonstrated in a scenario where scientific research has shown that there are new genetic variants that have been validated as being robustly linked to particular conditions. This may mean that patients who had previously opted out of receiving any incidental findings may now want to know whether they have these genetic alterations or vice versa.

It will be important to have further dialogue with patients about how they would feel if their genome sequence was being screened for a specific variant without their specific consent, or if they were not given the opportunity to modify their consent preferences to allow their sequence to be examined for a newly validated genetic variant.

We know from our study that the majority of patients are happy for their sequenced genome to be stored and re-analysed in the search for a diagnosis.

Further work would also need to be undertaken to determine the views of the patient community on whether they would have different preferences on incidental findings during re-analysis or whether they would welcome the continual re-analysis of their genome as part of an ongoing opportunistic screening programme.

“*We should have a choice, based on the fullest information we are able to understand, about all aspects of our health care. Standardised NHS criteria would deprive people of choice, could confuse some with too much information or insult others by withholding information. It would involve someone ‘playing God’ and deciding what we should know about our health, our bodies and our families.’*

**Recommendation:** Dynamic consent should be the standard model of consent when genome sequencing is used in clinical practice

**How to feed back results from genome sequencing**

For some patients, the results that could arise from having their genome sequenced will not come as a surprise, because of a family history of a condition or close correlation between their symptoms and a suspected diagnosis, for example. For other patients, however, the diagnosis they obtain may come as a shock. As a result of incidental findings or opportunistic screening, they may also receive other, unexpected information that they, along with their family, may not have previously considered or even have heard of. This could be directly related to the individual’s health or the health of their
family members, or may suggest that genetic relationships within a family are not what had been thought.

Having sufficient professional support throughout the process of genome sequencing is seen as crucial by the patients we asked in our study. Patients singled out genetic counselling as the most important thing they would like access to before making the decision about whether to have their genome sequenced. They also felt that it was an essential part of follow-up care. They agreed that counselling may be necessary in order to help them come to terms with a new diagnosis and/or to prepare for future treatments or prognosis. It may also be needed to provide advice about how a diagnosis may affect a patient’s children or siblings, or their decision-making around plans to have a family, and how best to communicate that information to their loved ones.

Given the sensitivity, and often complexity, of these discussions, it is reasonable for patients to expect that this aspect of their care would be delivered by a trained professional with knowledge of genomics and the ethical, social and practical issues that surround it.

A significant proportion (83%) of the patients that we questioned as part of this study have previously experienced genetic testing on the NHS, either as a patient or as a parent of a patient. From what they have already experienced of genetic services in the NHS, they agreed that genetic counsellors would be well placed to take on this role with respect to genome sequencing. Further recommendations that specifically relate to the patient perspective on genetic counselling and the demand for genetic counsellors can be found later in this document.

**Recommendation:** All findings from genome sequencing should be returned to patients by a trained professional, such as a genetic counsellor.
Background to genetic counselling in the NHS

As the cost of genome sequencing decreases and the technology begins to make its way into mainstream clinical practice, there are going to be more and more patients who are likely to have their genome sequenced as part of their NHS care in the hope of finding a diagnosis, or for other clinical purposes.

Genetic testing is widely used in the NHS to diagnose genetic conditions and there are a number of circumstances in which a clinician may request a genetic test for their patient. It may be prompted by symptoms of an undiagnosed condition that is thought to have a genetic cause, and patients who present with symptoms can be referred for genetic testing by a number of different healthcare professionals including paediatricians, neurologists and cardiologists. The aim of genetic testing is to confirm or rule out a suspected genetic condition, based on the patient’s symptoms. Often this is done by looking at one or two genes, or a small panel of genes and the result will be positive or negative.

Another situation in which a patient may be referred for genetic testing is if they have a family history of a genetic condition. In such circumstances patients may know of an affected family member or be caring for an affected loved one and be seeking information about the risk of developing the condition themselves or passing it on to their children or future children.

Genetic counselling is offered to patients both before having a genetic test and after. This gives patients the opportunity to talk through the consequences of potential results and the impact that these might have on their family or reproductive choices.

Once a genetic test has been done and the results received, a critical component of counselling is to help ensure that the individual patient and their family understand their test results and the implications.

Genetic counselling is well established as an essential step in the genetic testing process. As genome sequencing makes its way into clinical practice, it is inevitable that genetic counselling will become increasingly important due to the large number of patients that may undergo genome sequencing, but also because of the complexity and volume of information that may need to be explained to patients.

Genetic counselling and prenatal testing

The option of having a genetic test to diagnose a condition that a fetus may have inherited or acquired is a test that presents a particular need for good quality appropriate genetic counselling. In this scenario there is the added pressure of time, as a couple may wish to consider a termination following a prenatal genetic test result. In some circumstances there may be a protocol by which one member of the couple has a carrier test, followed by the second member, before making a decision about whether to choose to have a prenatal test. Genetic counselling around this form of testing must be delivered appropriately in a clear non-directive fashion at this particularly delicate moment in a couple's life.
Patient views on genetic counselling and genome sequencing

When we asked patients and families about what should happen before they decide whether to get their genome sequenced, the most popular response was genetic counselling, with over two thirds of participants selecting that option.

What information do you think it would be important to have before making a decision about whether to have your genome sequenced?

- What genetic counselling services will be available
- The results genome sequencing can reveal
- How the consent process works
- Details about who will be able to access genomic data
- How genome sequencing technology works
- An introduction to genetics
- Details about the implications for insurance

The value that patients put on genetic counselling gives a clear mandate to the health departments of the four governments of the UK to ensure that they make arrangements that will provide enough genetic counsellors trained to the required standard to meet the demand from patients for this service. This will ensure that all those being offered genome sequencing as part of their care on the NHS will have the opportunity to discuss with a trained professional the types of information that might be revealed and how that might affect their health and the health of their family.

The other information requirements that patients thought were important to receive ahead of making a decision about genome sequencing – such as how genome sequencing works, what the consent process is like, how their genomic data will be stored and used and the potential impact it may have on their health insurance – are all issues that could be dealt with effectively by a trained genetic counsellor.

“It’s complicated and people need to be given the opportunity to ask questions and have time to think about things.”

“A lot of people might have questions or worries and there ought to be a key person that you could talk to and relate to.”

Recommendation: All patients should be able to access a dedicated genetic counsellor before having their genome sequenced.
Training of genetic counsellors

There are currently around 300 genetic counsellors in the UK. There are two main training routes that can be taken in order to be a genetic counsellor. Graduate nurses or midwives with two years of post-registration experience must complete a counselling skills training course of at least 90 hours duration and a genetics course of at least 30 hours before being eligible to apply for a position as a genetic counsellor. Graduates with a degree related to clinical genetics such as genetics, biology, psychology or sociology, can apply to do a master’s degree in genetic counselling, which they must fund independently.

At the moment there are only two institutions in the UK that offer an accredited master’s degree in genetic counselling: the University of Manchester which has an intake of students every other year and Cardiff University which has an annual intake of students. These courses are both accredited by the Genetic Counselling Registration Board (GCRB).

Regulation of genetic counsellors

Given the often delicate information that genetic counsellors have to communicate, and the increased need for qualified professionals to meet the demand for counselling services, it is perhaps surprising that the profession is not currently recognised or regulated in line with similar clinical practitioners. Statutory regulation would ensure that all genetic counsellors had gone through rigorous testing, had to adhere to clinical practice guidelines and could be disciplined or struck off in the event of malpractice.

To illustrate the importance of statutory regulation of genetic counsellors, it is worth considering the perspective of a genetic counsellor through the eyes of a patient or family member who may be receiving information about a life-limiting condition. The majority of appointments with genetic counsellors are arranged by a regional genetics service following a referral from a referring practitioner. The patient will have received an appointment with a doctor, the subject of statutory regulation, and travelled to an NHS institution, following the same procedure that they would be used to.
to from previous appointments with nurses, doctors or midwives. Essentially an appointment with a
genetic counsellor strongly resembles a meeting with a statutorily regulated healthcare professional,
in terms of location, seriousness of situation and protocol. There is very little, if anything, to indicate to
the patient that they are no longer protected from malpractice in the same way that they might be
with other healthcare professionals.

In 2009, the Association of Genetic Nurses and Counsellors successfully applied to the Health & Care
Professionals Council to be statutorily regulated. In 2011, however, the Government stopped the
addition of aspirant professions to statutory regulation and introduced assured voluntary regulation. Genetic counsellors currently self-regulate under the GCRB and are not statutorily regulated but have recently applied for accredited voluntary regulation. The decision on this is still pending.

Discussion of the statutory regulation of genetic counsellors in Parliament

Asked by Lord Walton of Detchant on 18 November 2014: “To ask Her Majesty’s Government
whether, in view of developments in genomic medicine and the case for communicating accurately
and sensitively the significance of genomic data to patients, they will reconsider the possibility of
mandatory registration of genomic counsellors.”

Answered by the Parliamentary Under-Secretary of State, Department of Health (Earl Howe)
(Con) on 2 December 2014: “The Government has emphasised the importance of developing a
well-trained National Health Service work force to benefit from the advances in genomic medicine.
The education and training requirements of genetic counsellors and their regulatory arrangements
are currently being considered as part of the Health Education England’s Genomics Programme.
NHS England is focused on ensuring it fulfils its contribution to meeting the objectives of the
100,000 Genomes Project and the elements for which it is accountable. This includes establishing
NHS Genomic Medicine Centres through a robust procurement process, as part of which all
potential NHS Genomic Medicine Centres will be required to demonstrate what arrangements they
will put in place to ensure validated findings are fed back to patients in an appropriate and timely
manner.”

Genetic Alliance UK supports the work that is currently being done by the profession to self-regulate
but it would be desirable from a patients perspective to know that genetic counsellors are regulated
in the same way as the other health professionals that they come into contact with.

Recommendation: Statutory regulation of genetic counsellors needs to be
established to ensure the services delivered to patients and families are
appropriately assured

Educating genetic counsellors and other healthcare professionals about genomics

Traditionally, genetic counsellors have dealt with conditions related to single genetic alterations but as
genome sequencing becomes integrated in NHS care, genetic counsellors could find themselves more
frequently faced with genomic data.

This ‘genomic counselling’ is likely to mean that a larger amount of information related to health will
need to be communicated back to the patient, perhaps in just one session. As well as potentially
talking a patient and their family through the implications of a new diagnosis, or the absence of one
so far, a genetic counsellor may also be required to explain incidental and opportunistic findings. This
is likely to include genetic variants that are known to change the likelihood of an individual
developing a certain condition. This will require a genetic counsellor to explain how a genetic variant
can increase an individual’s risk of developing a condition without guaranteeing that they will develop it. Similarly, a genetic counsellor will need to explain why even though an individual may not have particular risk genes for breast cancer, cardiovascular disease or Alzheimer’s disease, for example, that they are not protected from developing these conditions. In some cases, the information that genetic counsellors will return to patients and families may include findings where a lack of scientific evidence means that the relevance to the patient’s health is unclear.

The volume and complexity of information from genome sequencing goes beyond that produced by most other genetic tests currently used in clinical practice. Therefore, the demands on a ‘genomic counsellor’ are likely to extend beyond the scope of the day-to-day work of most of today’s genetic counsellors. Additional specific training should be developed to ensure that counsellors are prepared for the specific skills that will be required to meet the needs of the patients who will be receiving the results of their genome sequence analysis.  

Recommendation: Training for genetic counsellors should include education on genomic information

The opportunities that genome sequencing presents for improving clinical outcomes are numerous and significant. The most immediate benefit that genome sequencing can offer for patients is as an additional tool for diagnosing rare genetic conditions. As has already been discussed in this document, genomic data can also provide information about how an individual’s risk of developing certain conditions in the future and whether they are a carrier of a heritable condition. But as we learn more about how our genes can affect our health we are likely to find new ways that genome sequencing can inform and improve our healthcare.

One application that has already been widely investigated is the use of genetic information to find out which medicines will and will not work for an individual, and what the most effective dose for that person might be. This is called ‘pharmacogenomics’. This notion already being applied to the delivery of some cancer treatments, on an individual level, as well as that of the tumour, but may in future also be applied to other medicines such as pain killers, for example.

Given that genome sequencing technologies are therefore likely to become an increasingly important aspect of our clinical care, health professionals who traditionally had no connection to clinical genetics will find themselves having to deal with genetic and genomic data. Health Education England (HEE) is the body responsible for ensuring that the NHS workforce is supported and equipped with the skills needed to provide a high-quality healthcare service. This is soon going to need to include being able to manage the type of data that will emerge from genome sequencing as it moves into mainstream clinical practice. The Genomics Education Programme that has been established by HEE to support the work of the 100,000 Genomes Project is therefore a welcome initiative and is a good example of how the 100,000 Genomes Project should help to secure a modern NHS that is educated, trained and equipped for today’s advances in genomics and those that could be developed in the future.

Recommendation: All healthcare professionals should be trained to have a basic understanding and knowledge of genetics and genomics
Patients welcome the sharing of their genomic data for research purposes

Background to the sharing and storage of genomic data for research

Genomic information has the potential to transform the health care system that we recognise today. Researchers are continually learning more about the genome and the genetic basis of disease, and as the cost of genome sequencing technologies and analytics tools decrease, more and more research will be possible. This will enable us to achieve a greater understanding of how our genes affect our health and develop new diagnostic tools, screening methodologies and therapeutic interventions for some conditions.

It is also hoped that a better understanding of the genetic basis for disease will allow for a more personalised healthcare system, where the drugs we take are tailored to what our genetic information says is likely to work best for us. This could help to avoid patients taking medicines that, because of their genetic make-up, are more likely to result in them experiencing serious side-effects than any clinical benefit. For cancer treatments in particular, looking at the genetic changes in a cancer tumour can be essential for ensuring that the most effective therapeutic regime is chosen.

In the future, other applications for the knowledge gained from research into our genome sequences may be identified, of which we currently cannot fully conceive. However, none of this will be possible without research into the human genome. This is likely to be advanced most rapidly by sequencing and analysing large numbers of complete genome sequences.

Patients and researchers have a mutually beneficial relationship. For many of the patients who took part in our study, research is their only hope of getting a diagnosis, of being able to access novel therapies and of benefiting from newly developed technologies – which at present includes genome sequencing. At the same time, research studies rely on being able to access and analyse patient data in order to make the advancements that patients so desperately want and need.

To enable this relationship to flourish, patients who want to participate in research need to be able to share their genomic data and feel confident that it will be stored and used appropriately.

For patients in the rare disease community, the need for patient data to be shared and used widely is not a new concept. Given the small number of individuals affected by rare conditions, patients recognise that collecting as much data as possible, often across international boundaries, is vital if enough information about their condition is to be made available to researchers in order for them to carry out meaningful studies. For these patients, not sharing data would be detrimental to research efforts and as a result, to the scientific advancements these patients and families look to for improvements to the quality and length of their own lives or the lives of their loved ones. One example of a research project like this is the DDD study.
The Deciphering Developmental Disorders (DDD) study

The aim of the DDD study is to use genome sequencing technologies in the hope of discovering the cause of developmental delay in children with undiagnosed conditions. 12,000 families are to be recruited to the project by April 2015 from across the UK and Republic of Ireland. A trio of samples for each family (child and both parents) will be analysed using genome-wide microarray and whole exome sequencing. This will be performed at the Wellcome Trust Sanger Institute.

Pertinent findings from the study are fed back to families via their geneticist or a genetic counsellor. They are then clinically validated in an NHS laboratory, which may involve providing another sample. The study does not currently feed back any additional findings to families, even if they are clinically actionable.

To date, the study has reported “a diagnostic yield of 27% among 1133 previously investigated yet undiagnosed children with developmental disorders”. 12 new developmental disorder genes have also been discovered.

As the number of samples to be analysed increases, the project team hopes that it will be able to distinguish further causes of developmental delay and provide more families with a diagnosis.

To continue to research the causes of developmental disorder, genomic data acquired as part of the study will be made available to researchers and clinicians via three routes, with varying levels of detail, patient information and access.21,22,23

Patient views on the storage and use of genomic data for research

There has been much public debate about the sharing of medical data for research in recent years and concerns over data security, privacy and access. This has included the electronic sharing of patient information collected in general practice as part of care.data, and more recently has considered the potential use and abuse of the genomic data that will collected as part of the 100,000 Genomes Project.

When we asked patients what they thought about the use of genomic data for research, 93% of participants said that they would want their genome sequences to be used for research purposes. As described above, this finding is perhaps not surprising given the nature of the patients and families that participated in this study. All participants are affected by a rare genetic condition, diagnosed or undiagnosed, either as a patient or as a parent of a patient. Therefore, they are perhaps more likely than most to appreciate the value of data sharing for research and be more comfortable with their personal information being used for this purpose.

Those with rare genetic conditions are more familiar with the relative ease with which they can be personally identified from their medical records, due to the small number of people affected by their condition. This perhaps explains why our respondents felt it less necessary for their genomic information to be completely anonymised before being shared with researchers and were relaxed about pseudonymised data being used in research.

Would you like your sequenced genome to be made available for research?

- Yes
- I’m unsure
- No

“Isn’t good to share for the good of others.”
When we further asked patients and families whether their views on sharing their genomic information for research was dependent on the type of organisation that would be undertaking that research, there were some interesting differences. Over two thirds of respondents were happy for the NHS (80%), universities (77%) and charities (63%) to use their data for research purposes. The fact that the majority of respondents supported genomic research within the NHS is as a clear endorsement from our patient community that they welcome current and future initiatives that put the NHS at the heart of this type of research. In contrast, 38% of respondents said that they were comfortable with private companies using their data and only 31% would trust government institutions to use their data for research.

The main reason participants gave for their disinclination to share genomic data with private companies was that they weren’t comfortable with the fact that such companies had the potential to make profit from research that involved their data. They found this particularly concerning because patients and families affected by rare genetic conditions can face significant financial pressure as a result of a condition, such as being unable to work or needing to pay for additional care or equipment. Comments from participants indicated that the reason why many of them would not share their genomic information with governmental institutions was because they could not see a good reason why they would want to use it. Others noted their concerns that they did not feel confident that government would be able to ensure that their genomic information would be kept private and secure.

Another issue that raised particular concern among respondents was about their genomic information being accessed by insurance companies. There is a moratorium on the use of genetic data for insurance purposes in the UK, which defines the very limited scenario in which genetic information needs to be disclosed to insurers. This was extended to 2019 and updated in December 2014 to include a specific clarification that results from genome sequencing research projects do not need to be disclosed to insurers.24

**Recommendation:** The NHS should take steps to enable the safe storage and sharing of patients’ genomic sequence data to maximise research opportunities.
Our study also revealed that patients feel that it is important to have control over their genomic data and how it is used for research purposes. Patients overwhelmingly supported the use of dynamic consent in a research setting in the same way as they value autonomy and choice about how their genomic data will be used and what they find out from it in a clinical context. This indicates that patients and the public may feel more comfortable about allowing their data to be used in research if they knew they had the ability to change their preferences and opt out, or in, whenever they saw fit. This finding fits with our earlier recommendations regarding dynamic consent.

Supporting further research into newly diagnosed conditions
We know from working with our patient group membership and the SWAN UK community that a timely, accurate diagnosis is crucial for all those affected by genetic conditions. Answers finally begin to be delivered to individuals and families who, up to that point, have had only questions.

Knowing that you or your child is ill but not knowing why can be incredibly distressing for patients and their families. In addition to this, an incorrect or absent diagnoses can be associated with significant clinical risk, such as the delivery of an inappropriate treatment or intervention, or avoidable delays in arresting the progress of a treatable condition.

Getting a diagnosis can be the critical step required in order to be able to access the most appropriate treatment and services for your condition. It can give you an indication of what to expect: how the condition may progress and when you may need to make decisions about your future health and care. We know also from the SWAN UK community that families often value a diagnosis even when this does not lead to new therapeutic options. Being able to give a name for your child’s condition can allow you to open the doors that will enable access to specialised care services or educational support. For many it can also just mean being able to plan for the future or finally put to bed the guilt that many parents can feel that what their child is experiencing is the result of something that they have done wrong. Despite the focus that many families have on getting a diagnosis for their child, it is rarely the final hurdle. Often, the reason that it takes so long for patients to be diagnosed is because the condition they are affected by is very rare. In some cases a patient may be the first person in the world to be diagnosed with a particular presentation of a defined condition or the only person known to have symptoms associated with a specific genetic alteration.

As a result, rather than a diagnosis providing the answer to the questions that patients and their families may have, it can mean the end of the road in terms of further information. In an ideal world, being diagnosed with a rare condition should bring all the benefits that other patients get from being diagnosed with more common conditions. This can only be achieved by supporting further research into newly diagnosed conditions. Specifically, the investigation of how a genetic diagnosis may translate into the length and quality of a patient’s life and the development of new treatments.

With the 100,000 Genomes Project taking off in England, the research community will be thinking about how best to utilise the data that emerges from the project in order to gain a better understanding of rare conditions and identify opportunities for therapeutic intervention. Genomics England have proposed the formation of Clinical Interpretation Partnership (GeCIP) domains as a way for funders, researchers, trainees and clinicians to collaborate and form communities related to specific diseases or genes. It would be valuable for GeCIP to also address the specific investigation of
those unique or exceptionally rare genetic conditions in order to start being able to establish useful information for the patients and families that receive this as their diagnosis.

**Recommendation:** Research to better understand newly identified conditions, investigate potential treatments and define prognoses should be incentivised

**Discussing the dividing line between research and clinical care**

A distinction has often been made between clinical care and research studies in terms of the ethical principles that govern them, their legal obligations and the type of body or institution that undertakes them. Recent work from the PHG Foundation has supported maintaining this distinction. They concluded that: "There was support for a model of practice that enabled both clinical care and research to be done in parallel, but not for a distinct category or hybrid activity in which clinical and research elements were indistinguishable from an ethical and regulatory perspective."25 As genomic technologies develop and become more widely used in clinical practice, however, the boundary between these seemingly separate activities from the perspective of the patient is becoming increasingly blurred.

The amount of information that can be gained from genome sequence data in terms of defining an individual’s current or future health and care needs is considerable. While this information is currently only being gathered for a small number of individuals through defined research or pilot studies (such as the 100,000 Genomes Project and the DDD study), the outcomes of this work have the potential to directly affect the treatments and therapies that these individuals may receive. It is easy to see how patients think it can be difficult to see any distinction between genomics in research and clinical care.

As an example, let us consider a family whose child is part of the DDD study, a research project. The family will be taking part in the study because they are seeking a diagnosis for their child’s condition. The family will have been referred to the project by a clinician from their regional genetics centre as current genetic testing through the NHS has thus far not yielded a diagnosis. If the DDD study yields any results then they will be fed back to the family through their geneticist or genetic counsellor, as part of the clinical consultation process. If genome sequencing yields a clinically significant result for these patients and families then they are unlikely to be concerned with whether the result arose as part of their clinical care or through a research study. Whether patients and families do distinguish between clinical and research activities is perhaps less important than how differences between how these different types of study are regulated and how that may affect the disclosure of results to patients.

If studies such as DDD, which straddle the boundaries of research and clinical care continue to take place, then it is important to consider how any variation that exists between the consent processes and/or the type of information that will be disclosed can be effectively managed. These issues are of particular importance in light of our study, which asked patients and families whether their willingness to participate in research was dependent on their ability to benefit from the technology i.e. on getting a diagnosis for themselves or their child.
For just over a quarter of respondents, they would only share their genome sequence for research if it had enabled them to obtain a diagnosis. While the majority of respondents would still be willing to share their genomic data for research regardless of any personal benefit, the finding raises the interesting issue of when a research study becomes clinical care and vice versa. If a genome is sequenced as part of clinical care, for example, does that mean that it is made immediately available for research or only once it has served its clinical purpose?

Consideration of where it would be most appropriate to draw the line between research and clinical care raises a number of other interesting issues: Given that the same type of finding can be identified in both a research and clinical context, should the availability of genetic counselling services be equivalent in both contexts? If findings that have the potential to affect individual’s current or future healthcare needs will be disclosed to research participants, how is the subsequent requirement for clinical care going to be managed? Should patients and families consent for both the clinical and research applications of genome sequencing simultaneously, or would this mean that the process becomes too confusing and burdensome for patients and clinicians? This nuanced interface between clinical care and research in genome sequencing, and to what extent this could be addressed through dynamic consent, deserves further consideration.

**Recommendation:** Research studies and clinical care involving genome sequencing should be more closely integrated to reflect the patient experience.
Patients think that the NHS needs to make more progress towards preparing for the integration of genome sequencing into clinical practice

Background on patient views on genome sequencing in the NHS

The patients and families we engaged with during our study are overwhelmingly enthusiastic about genome sequencing and the potential for it to be used as part of their NHS care. 87% of our study participants said that they think genome sequencing would be helpful to themselves or their child if it were offered to them today and 94% said that they were either “very likely” or “quite likely” to give their consent.

For many of the patients and families questioned, this will be because either themselves or their child are still seeking a diagnosis for their condition. Indeed, those participants who said they were “not very likely” to consent to genome sequencing gave their reason as being that they already have a diagnosis for their condition and could see no extra benefit that genome sequencing could offer them. Many of the participants in our study did have a diagnosis for their condition, however, indicating that for at least some respondents, their interest in genome sequencing is not just about its diagnostic potential but also because this technology is capable of revealing other types of information.

This indicates that there is a clear appetite for genome sequencing to be incorporated into clinical care as an additional clinical tool through which patients can be diagnosed in an accurate and timely way. But more than this, it suggests that there is a strong interest from this group of patients and families, which may be echoed by the public more broadly, in the other opportunities that genome sequencing provides. In the near future this could include providing more detailed information about an individual’s risk of developing certain conditions or by enabling the type and dosage of medicines given to be tailored to an individual’s genetic make-up. It will be important to determine the perspective of patients and the wider public on these types of scientific development and the potential for them to become a clinical reality within the NHS.
The complexities of talking about genome sequencing in the NHS

How easy do you think it is to explain genome sequencing to people in a way that enables them to make an informed decision about whether to have their genome sequenced or not?

While there is considerable support from the patients and families we questioned for genome sequencing to be used as part of NHS care, there were also some concerns raised. In particular, they told us that they did not think there was enough information available for patients about what genome sequencing is, how it works or the different types of results that it could be reveal.

It is clear that there is an interest and a need for more information about genome sequencing from the patients most likely to come into contact with this technology as it is introduced in the NHS. It is therefore important to note that when we asked how easy it is to explain genome sequencing to people in a way that would enable them to make an informed decision about whether to consent to having their genome sequenced or not, over half of the participants said that they thought it was either “difficult” or “very difficult”. This was after they had completed all of our online engagement activities, which sought to explain genome sequencing and all the associated information in a clear and concise way. Many of our participants told us that our online engagement sessions were the first time that they had heard of genome sequencing.

Before we started our online sessions about genome sequencing, we asked patients whether they had any concerns about having their genome sequenced. This revealed that a large number of patients were concerned about people accessing their/their child’s personal genetic information or finding out things about their health that they weren’t expecting. They were also worried that the technology may not be completely accurate. Additionally, the issue of insurance companies accessing patient data was raised throughout the project as patients were worried that they might be stigmatised and unable to access insurance products because of a result of genome sequencing.

“I feel that in our unique family of five children with a very novel form of epilepsy and many other issues that genome sequencing is our only avenue left to explore. My five children all have epilepsy, autism and learning difficulties. By taking part in a research study we now know which mutation is causing the problems for three of my children. It’s a novel gene and our clinician is currently searching for another person in the world living with the same mutation. We don’t yet have a proper diagnosis for my other two children although their symptoms are the same as the other three. Currently we don’t have any answers for the future to be able to get targeted treatment, therapies, education and care packages, which are so desperately needed here!”
This identifies a variety of areas that patients and families would specifically welcome information on. It will be important to explain what genome sequencing can and can’t tell a patient about their health; who will be returning any results they get from genome sequencing to them; how these results may affect their health or the health of the loved ones and that this information may be unexpected. It will also be important to provide details of how their genomic data would be stored and who it will be shared with. If this will include the use of their data for research, this will need to be specifically indicated and the nature of the research explained. It is also clear that patients will want to be informed about the relationship between the information revealed through genome sequencing and what they may need to disclose to insurance companies.

Our respondents felt that without access to all this information it would not be possible for a patient to give informed consent. They also felt that the consent process itself should be made clear to patients so that they appreciate its pivotal role in determining how much and what type of information you may receive back about your genomic sequence.

The breadth and complexity of this information, along with the perceived difficulty of explaining genome sequencing and its associated issues, underscore the importance of having accurate and comprehensive information available to patients. As mentioned elsewhere in this document, genetic counsellors are well positioned to provide this information to patients, answer any questions or address any concerns that patients may have. However, this is only available to them once in they are in the clinical system or within a research study already. Therefore, the information that patients are able to access in their own time, from the comfort of their own homes, is also crucial. In order to ensure that the

Genetics and insurance

If you’re experiencing symptoms of a genetic condition then you need to explain this to your insurer. You do not, however, have to disclose the results of predictive genetic tests (tests which will tell you how likely you are to develop a genetic condition in the future). The only exception is if you have taken the test for Huntington’s disease and you are applying for a life insurance policy of over £500,000 or a critical illness policy of over £300,000. Your insurer may ask you whether you have a family history of a particular condition and if you’re aware of one then you must tell them. However, if you have a family history of a genetic condition and have taken a predictive test which has shown that you will not develop the condition then you may wish to tell your insurer. 26
information produced covers all the necessary topics, at the most appropriate level of detail and in the most user-friendly format, it will be necessary to work collaboratively with patients, patient groups and the wider public.

Recommendation: The NHS should engage with the patient community to develop accurate and comprehensive information on genome sequencing

Access to genome sequencing across the UK
It is likely that genome sequencing will become part of clinical practice across the UK in the future. But the speed and uniformity with which this will take place across the UK, will need to be carefully planned and managed to ensure equitable access for patients.

Genomics England has been established by the Department of Health to deliver the 100,000 Genomes Project in England. This means around 75,000 patients will have their genomes sequenced by the end of 2017 with the aim of advancing knowledge in the fields of cancer, infectious diseases and rare diseases. In addition to research into particular conditions, the 100,000 Genomes Project aims to set up a genomics medicine service for the NHS that will continue to function beyond the end of the project itself.

In January 2015, the Scottish government announced that they were making a major investment in genome sequencing technology. The £15 million project will see the universities of Edinburgh and Glasgow partner with Illumina to establish The Scottish Genomes Partnership. The initiative will enable scientists and clinicians to access equipment that can decode the entire genetic make-up of a person for less that £750.27

The Welsh Government have committed to working with a number of NHS, university and industry partners to produce a proposal for development of infrastructure for genomic medicine in Wales. The Implementation Plan for Rare Diseases also committed stakeholders to a number of new initiatives to improve access to diagnostic testing and genomic sequencing technologies. These commitments include a review of resources for genetic services to provide equity of access for Welsh patients (conducted by the All Wales Medical Genetics Services and Welsh Health Specialised Services Committee). This will also devise a system for assessing new tests and the funding required to support them. It is essential that any proposal is developed in a timely and robust way, considering other initiatives currently underway in other parts of the UK and where it is appropriate, a collaborative approach to advances in genomic medicine services.28

In Northern Ireland, responses to the consultation on the Rare Disease Implementation Plan (RDIP), which closed on 19 January 2015, are under consideration. The process highlighted the importance attached by citizens of Northern Ireland to genetic advances in diagnosis, management and treatment of rare conditions. This is further evidenced by involvement with initiatives such as the DDD study, where Northern Ireland’s record of recruitment demonstrates the high level of family and patient support for this type of groundbreaking research. Northern Ireland’s model for participation in the 100,000 Genomes Project and in other precision medicine initiatives is being considered in the context of the RDIP. Clinicians and researchers in Northern Ireland are participating in UK-wide clinical interpretation partnerships for the 100,000 Genomes Project and several applications have been submitted for consideration.29

While these independent initiatives should be welcomed, we should recognise the benefits of taking a more coordinated approach across the UK. We know from our work on access to specialised services and treatments (the category that genome sequencing is most likely to fall into in the first instance), that it can be hard for rare disease patients to access the same level of service across the UK. 30
Ensuring that all those patients who could benefit from the technology in the UK are able to access it should be a priority for the NHS.

The core ideals of the NHS are that its services meet the needs of everyone, are free at the point of delivery and that healthcare should be based on clinical need.\textsuperscript{31} With this in mind, when genome sequencing becomes part of NHS care, it should be free to those who could benefit from it.

We asked patients and families to tell us how much they would be willing to pay for genome sequencing for diagnostic purposes, in order to ascribe the value that they place on this technology. Less than a quarter of respondents said that they would not be willing to pay for genome sequencing as part of their NHS care while over 40\% of said that they would pay over £100.

The fact that many patients would be willing to pay to have their genome sequenced indicates the desire from patients for this technology. The NHS will need to recognise that if it does not start to incorporate genome sequencing into clinical care then patients and families are very likely to seek access to these technologies in a private capacity. It cannot be guaranteed that patients who have their genome sequenced in this way will receive the appropriate support from a genetic counsellor or other trained professional in order for them to be prepared for or able to appreciate the implications of what their genome reveals. It may also be possible that a patient becomes falsely reassured from the outcome of a private genome sequencing company if the analysis carried out is not as rigorous as possible. In both of these scenarios, and many similar ones, the NHS will need to be able to manage the consequences of genomic sequencing data where it directly affects patient health, even if they are not the provider. The NHS should therefore work to ensure that patients and the public can feel confident that it will offer genome sequencing where it can provide patient benefit, with no associated cost.
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