JOHANNA H. BIJTEL CHAIR

Anneke Lucassen MD PhD

From mutation to relation:

THE CHALLENGES OF PERSONALISED MEDICINE IN THE GENOMIC AGE

From mutation to relation

The challenges of personalised medicine in the genomic age

Anneke Lucassen

Public lecture as professor in the Johanna H Bijtel Chair 2014 - 2016, October 2014

rijksuniversiteit groningen

umcg

From mutation to relation: The challenges of personalised medicine in the genomic age

The ability to analyse a human genome- a person's entire genetic code- has increased in speed, and decreased in cost by about a million fold over the last 2 decades. It is now possible to routinely analyse a person's entire genetic code at a cost affordable to many health care services. This has led to much optimism about the ability to personalise approaches to health care based on the particular characteristics of a genome. Whilst much of this excitement is appropriate; there have been some fantastic examples of stratifying treatments (or of directed interventions according to genetic variants), there has also been much hype and some unrealistic expectations of what a genome result can ever expect to predict.

I want to have a closer look at this area between a genome sequence and its interpretation. Not because I want to claim that excitement about advances in genomics is inappropriate, but rather because I think the only way that these advances can be appropriately integrated into health care is to look more closely at some of the potential barriers to implementation. In doing so I want to suggest some of the ways that we can have more realistic expectations of what genomics will mean for health care and how we might handle some of the tensions. For example, the more we are indeed able to personalise genomics, the more we have to think about genetic relatives who might share this personalised information and who may also benefit from such knowledge. Health care practice in the western world is generally uncomfortable in considering a patient's relations as part of the clinical encounter or as individuals who might also need to be communicated with. Furthermore, whilst personalising medicine sounds appealing, it is something that physicians have sought to do since Hippocrates; to personalise the approach and treatment according to the needs and wishes of the patients. This aspiration has not arrived with the genomic revolution. I suggest that genomics allows vastly improved *stratification* of health care approaches but that personalisation is not particularly facilitated by knowledge of a person's genetic code, because that genetic code is inevitably shared with others.

My journey to Bijtel

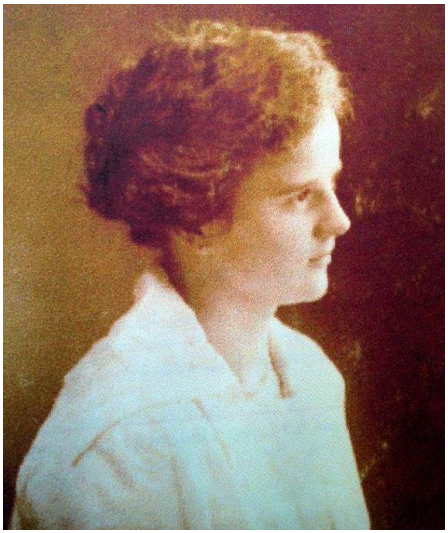


Figure 1 Rens Remmers

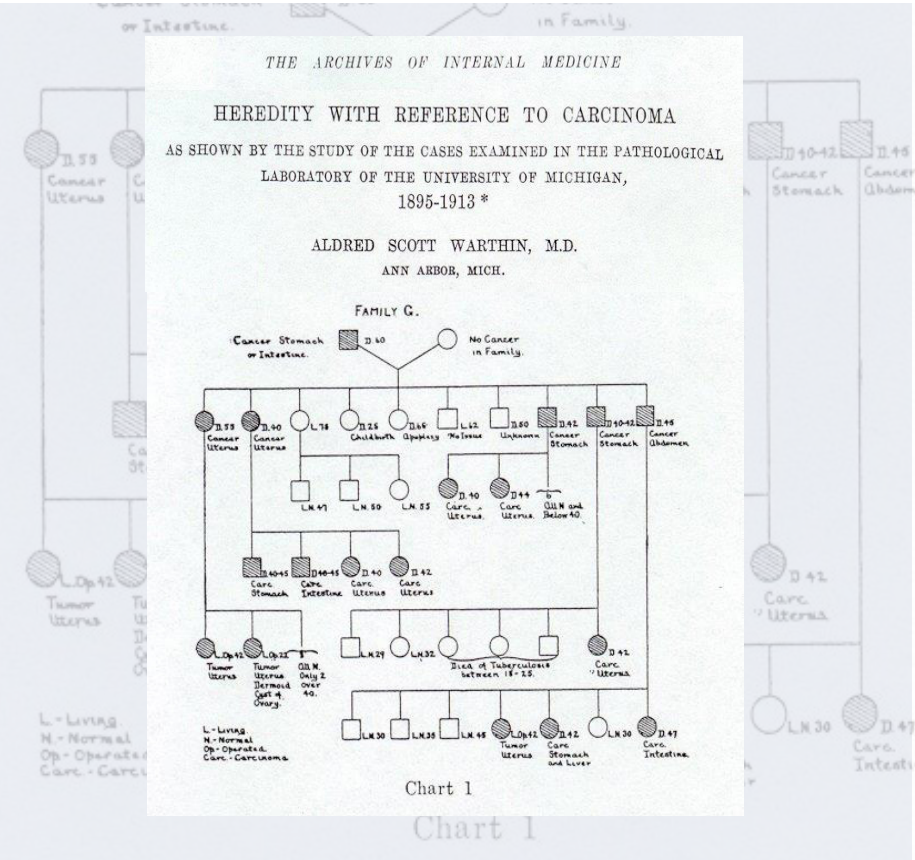
My journey to the Johanna Bijtel chair was perhaps more fated than the chance remark from Prof dr Irene van Langen via email "might this be of interest?" would suggest. Johanna Bijtel was born in 1898 and was an unusually emancipated woman for her time. My maternal grandmother, Emerentiana ('Rens') Remmers (see figure 1) was born in 1893 in Groningen. She was the 5th of 8 children born to a relatively poor tailor who lived in the Martinikerkhof, number 31, a house that still stands today. Figure 2 shows a painting of her by my maternal grandfather juxtapositioned next to Johanna Bijtel.

They look quite similar I think, but despite being contempories, they are unlikely ever to have met since my grandmother left Groningen at the age of 17. Due to the patronage of a friend of the family she was sent to Harlingen to learn to be a school teacher. This early independence and the onset of the first world war creating opportunities for women to teach on a scale not previously possible, meant that she was the first emancipated woman in my family.

In my grandmother's year of birth a famous Dutch botanist, Hugo de Vries published a treatise on genetics. He is widely credited with picking up genetics where Gregor Mendel left off some 50 years earlier, and as the first person to describe a unit of inheritance as a 'gene', and the term 'mutation' for a new variation in these units of inheritance. That mutations causing cancer might be inherited through families was also first described around this time. In 1895 Warthin first came across a family in which bowel, womb and other cancers appeared at a strikingly young age (See Figure 3). It was not for another 100 years, however, that the exact mechanism of this inheritance would be understood.

My own journey in genetics started almost exactly one hundred years after Warthin first described this family. After my general medical training in Newcastle and Oxford, I

Figure 2 My grandmother born 1893 next to Johanna Bijtel born 1898



THE ARCHIVES OF INTERNAL MEDICINE

HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN, 1895-1913 *

ALDRED SCOTT WARTHIN, M.D.
ANN ARBOR, MICH.

FAMILY G.

Chart 1

Chart 1

FIGURE 3 FAMILY TREE OF FAMILY WITH HERITABLE CANCERS DESCRIBED BY WARTHIN

worked on a beautiful Island in the south pacific -Vanuatu- exploring the relationship between an inherited condition -thalassaemia- and the environment. Mild forms of the condition (or being a carrier of the condition) appeared to protect against malaria and I was part of a clinical research project examining why. This gene-environment interaction seemed exciting and a sharp contrast to my somewhat uninspiring undergraduate lectures on genetics. I became interested in this new and emerging field and went back to Oxford just at a time when genetic technologies were rapidly taking off. Armed with a Wellcome Trust Clinical training fellowship, I did a PhD (DPhil as it is called in Oxford) at the Weatherall Institute of Molecular Medicine in John (now professor Sir John) Bell's laboratory, identifying some of the genetic factors that result in susceptibility to diabetes. This was an exciting time, with lots of new discoveries, and I identified several genetic variants that increased the chances of someone developing Type 1 (insulin dependent) diabetes which were published in journals such as Nature Genetics and the American Journal of Human Genetics[1].

[1] For example: A.M. Lucassen, C. Julier, J. P. Beressi, et al. Susceptibility to insulin dependent diabetes mellitus maps to a 4.1 Kb segment of DNA spanning the insulin gene and associated VNTR. Nature Genet 1993: 4, 305-310/ S. T. Bennett, A. M. Lucassen, S.C.L. Gough, et al: Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. Nature Genet 1995 9, 284-292 / A.M. Lucassen, G. Screaton, C. Julier, et al. Regulation of insulin gene expression by the IDDM associated, insulin locus haplotype. Hum Molec Genet 1995, 4 (4), 501-506

I recently looked back at my PhD thesis and found that I had written some very enthusiastic predictions that:

(a) "The technological challenges of defining all the genes involved in common complex disease are rapidly being met" and

(b) "Once a gene has been identified, screening tests can be rapidly transferred to the clinical setting".

Twenty years later these have been proven to be wildly optimistic. None of my diabetes gene discoveries has been translated into the clinical setting. They have shed useful insights into the aetiology of the disease and on a population level are clearly associated with risks, but on an individual level their predictive value is too poor to be clinically useful. In my thesis I also commented that:

(c) "However these are susceptibility factors rather than causes, it is not clear how these loci interact... or what the impact of such information will be... there are also potential problems".

This latter prediction has turned out to be more realistic and has also become the area that I have developed my research attention to. What is the impact of these genetic discoveries? What do people think? What are the potential problems and what might their solutions be?

So I went from the laboratory to complete my training as a medical specialist. I set up a new clinical service in Oxford to advise those with a family history of cancer. This was new because it had just become possible to test for the genes that Warthin had described some 100 years earlier through a blood test. Genes that, when mutated, caused a very high lifetime chance of e.g. breast, ovarian, bowel and uterine cancer were isolated in the 1990s and determining who had and had not inherited these mutations made a big difference to the medical management of some families. Cancer genetics rapidly became a subspeciality of clinical genetics, advising those with a family history of cancer whether or not they had inherited a strong predisposition to particular cancers. Recently the actor Angelina Jolie - and other celebrities - have brought this sort of service to the headlines, but at the time very little known was known about familial cancers.

It turns out that inherited single gene mutations explain about 5% of all common cancers. That is, for every 100 bowel cancers, for example, about 5 have been largely caused by the inheritance of a particular gene mutation. Clues to the presence of such mutations in families are: whether there is a particularly strong family history of cancer, that is seen in successive generations, and whether certain types predominate particularly at a young age. Initially, we thought it was just a matter of time before other "strong" genes would be found, and a much greater proportion than 5% would be explained. Since then it has become clear that most of the remaining 95% of cancers are not due to a single inherited factor, but rather due to a combination of different weak genetic factors as well as environmental, epigenetic, or random factors. Like the factors I discovered for diabetes, each individually has very little clinical usefulness because on their own they predict disease too weakly to be able to act on with any certainty in the clinic. The next step is to reliably identify which particular combinations of genetic- and other- factors are necessary for a disease to manifest, and this to date has proved far more elusive than my 1995 prediction suggested.

A very short primer on genetics and explanation of terms

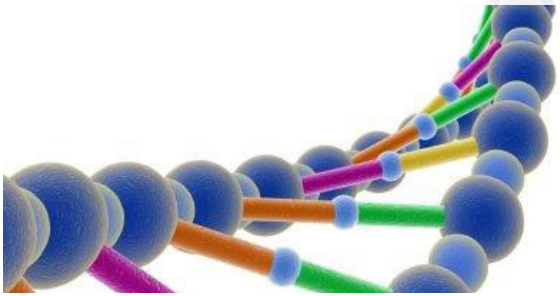


Figure 4 Double stranded DNA, the coloured pegs represent the different base pairs, G, A, T, C

Almost every cell in the human body has a nucleus which contains the same copy of our inherited genetic material. Twenty three pairs of chromosomes lie within the nucleus and each are tightly coiled sections of our genetic information. The chromosomes are found in pairs, one inherited from each parent, and only one passed on when we in turn have children. If each chromosome is unwound, you end up with the so-called double helix of DNA, pictured in figure 4. The coloured pegs are 4 different bases each annotated with a letter, which hold the strands together. It is the sequence of these letters that determines much of what happens in our bodies. The total length of sequence per cell is a **genome** (a fusion of the term gene and chromosome) and comprises about 3 billion DNA letters. A chromosome is a large chunk of DNA and smaller sections within this are **genes**. All the twenty thousand or so genes within the DNA comprise an **exome**.

Broadly speaking, genes send a message or signal which, if altered by a mutation, can result in problems the degree of which depends on the type and location of the mutation. Genes- or the sections of code between them- can also just be different between different people, without consequences for health. The study of this variation is the basis of, for example, criminal DNA fingerprinting. Older textbooks on genetics talk about either disease causing mutations or benign variation (polymorphisms). We now know there are all sorts of gradations in between these extremes where a genetic variation may have a disease risk in certain environments or in combinations with certain factors, yet not others. Figure 5 illustrates the degree of genetic variation in our genetic code. Humans have genetic codes that are roughly 99.9% identical; we vary in only 0.1% of our genetic code. My maternal grandmother and I were slightly more similar- roughly 99.925% identical. It is in this 0.1% that some of the explanation for differences in disease predispositions can be found, but not all. Building up an understanding of how such predisposition works is complex and much slower than the advances in technology that allow the code to be sequenced. A fruit machine where the jackpot combination is unknown can serve as an analogy. Only a particular combination of multiple factors results in disease; individual genetic factors may increase the chance of developing a disease in a population, but at an individual level it is all about which other factors you also have. You may need a particular combination of say, 10 factors and if you only have 9 you will not develop the disease. Some of these 10 factors may be environmental or epigenetic ones, so knowing the genetic code factors of the fruit machine will not necessarily tell you whether you will develop the condition in question. We know far too little about these interactions yet to utilise genomes to predict disease accurately. Another way of visualising this is by thinking of a genome as an iceberg; the tip that

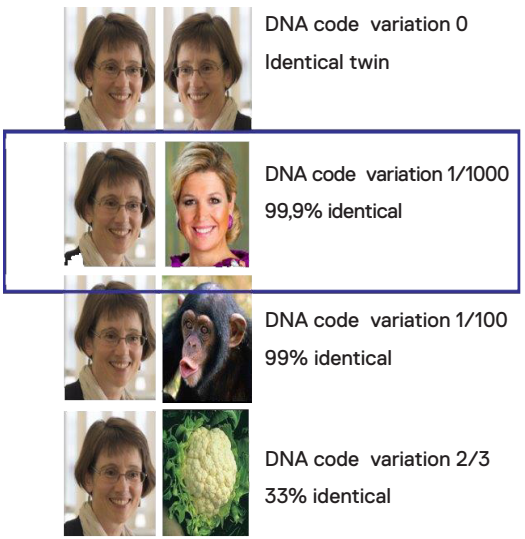


Figure 5 Average differences in the genetic code between me and (a) my identical twin (b) Queen Maxima (c) a chimpanzee and (d) a cauliflower

is visible is the part of the genome that are obvious; a man with achondroplasia has a particular mutation in his genome, a woman with thousands of polyps throughout her gastrointestinal tract will likely have a mutation in a gene called APC. That is, certain genes come to attention usually through signs symptoms or family history. Underneath the water lies the un-interpreted or uninterpretable genetic code. Although this is getting smaller as the ice is melting, there is still a lot that - in 2014 - we cannot interpret into useful clinical information.

So what are some of the issues that need to be considered as the technology leaps ahead? Or, how do we address the gap between the sequence and its interpretation? Firstly, we need more widespread acknowledgement of that gap. It is still commonplace that patients and health professionals alike assume that if only they knew the genetic code, predictions of health and disease will automatically follow. There is much less certainty associated with much of the 'readout' than commonly perceived. A recent New York Times article illustrated this well with the headline "finding risks, not answers, in gene tests" which described a patient wanting to determine her risk of breast cancer through genetic testing[2]. She was offered a newer panel test of multiple breast cancer genes instead of just the two very high risk genes BRCA1 and BRCA2. She had thought that the more genes tested, the more comprehensive her result would be, but she found to her surprise that the result introduced more uncertainty and difficult choices for her. I see this played out in my clinic regularly but it often comes as a surprise since the media portrayal of genetics has been one that makes genetic predictions seem straightforward and clear. We simply do not know how to interpret much of the output from genomic testing. Some variation found in an analysis might be a novel explanation for a rare disease or it might be normal population variation- or somewhere in between these two extremes. So what is a patient to do whilst we do not know? Do they undergo perhaps expensive/ painful/ risky interventions as preventative or surveillance options whilst awaiting further information?

Whilst we await the integration of large-scale bioinformatic approaches, interpreting the predictive value of a new finding in the clinic often relies on investigating family members. Does the variant found track with disease in that family? Is it found in lots of older family members without any ill effects? This can be a very effective way of gaining insight into pathogenicity but it does rely on communication within a family and testing of people who are not patients and may have no idea why they are being invited to be tested. This can in turn lead to issues around consent and confidentiality within a family, more of which later. How should this sort of family tracing - and its results - be recorded in a patient's medical records? Is this an example of familial medicine in order to personalise medicine? Table 1 highlights some of the issues that need to be considered when attempts are made to use genomics to personalise medicine.

These issues have interested me over the past 20 years. I have deliberately sought to combine my molecular genetic experience in the laboratory with a busy clinical genetic practice to examine and opine on the ethical, legal and social issues that are raised. Aside from my connection with Groningen through my grandmother, I had already forged another connection well before the Bijtel opportunity came up, when I wrote a book with Prof Marian Verkerk[3] - professor of ethics at the university of Groningen- and others, about a case direct from my experience in the clinic and the difficult issues involved in communicating genetic findings in one person to others to whom it might be relevant. The case was then viewed through the lens of a range of different ethical and legal experts and this multidisciplinary approach gave perspectives I had not before seen in clinical practice.

Looking at the interests (of a range of family members) in knowing the result in a relative is relatively unusual for modern medical practice. Whilst contact tracing for infectious diseases, or alerting the vehicle licensing authorities that a person is posing a risk to others by driving against medical advice, are more familiar reasons to stray from the individual patient-health professional relationship, these are usually justified on the basis of a clear and imminent risk to others, something that can be much less obvious when it comes to genomic results.

[2] "finding risks, not answers, in gene tests" New York Times September 2014
[3] Alternative approaches to bioethics. Case analysis in clinical ethics. Eds: R. Ashcroft, A. Lucassen, M. Parker, M. Verkerk G.Widershoven. Cambridge University Press 2005. ISBN-13:9780521543156 (see figure 6)

Table 1

SOME OF THE ISSUES THAT NEED TO BE CONSIDERED IN ATTEMPTS TO PERSONALISE MEDICINE THROUGH GENOMICS[4]

1	Distinguishing clinical utility of different "readouts". There is much less certainty in genome readouts than commonly perceived.
2	Clinical utility of test may *depend* on result in others[5]: Tracking of genotypes with phenotype. This raises issues around communication/ record keeping/ consent and confidentiality. It may also reveal that biological relationships are not the same as social relationships, and this may come as a surprise to some.[6]
3	Where a genetic prediction is clear, it may (therefore) also reveal predictions about the future health of family members. How should this be managed?
4	New technologies are changing genetics: We are moving from targeted testing to "trawling" of the genetic code. Trawling is cheaper and more efficient but results in a greater chance of finding 'incidental' 'unexpected' or 'secondary' findings- findings that are unrelated to the reason for the test. Can someone truly consent -or refuse- to hear about complete unknowns?
5	Far-off predictions are difficult for health care systems. Genomic test can provide a permanent result about inherited genetic code abnormalities but with usually at least some uncertainty about whether a condition will manifest. When should such information be revealed? How can health systems record such information in a way where re-contact can be made when interventions are available?

[4] Lucassen A, Houlston RS. The challenges of genome analysis in the health care setting. Genes (Basel). 2014 Jul 22;5(3):576-85. doi: 10.3390/genes5030576.
[5] Crawford G, Foulds N, Fenwick A, Hallowell N, Lucassen A Genetic medicine and incidental findings: it is more complicated than deciding whether to disclose or not. Genet Med. 2013 Nov;15(11):896-9. doi: 10.1038/gim.2013.165. Epub 2013 Oct 3
[6] A.M. Lucassen and M. Parker. 2001 Talking about paternity in the genetic clinic: Some ethical considerations Lancet 357 1033-56

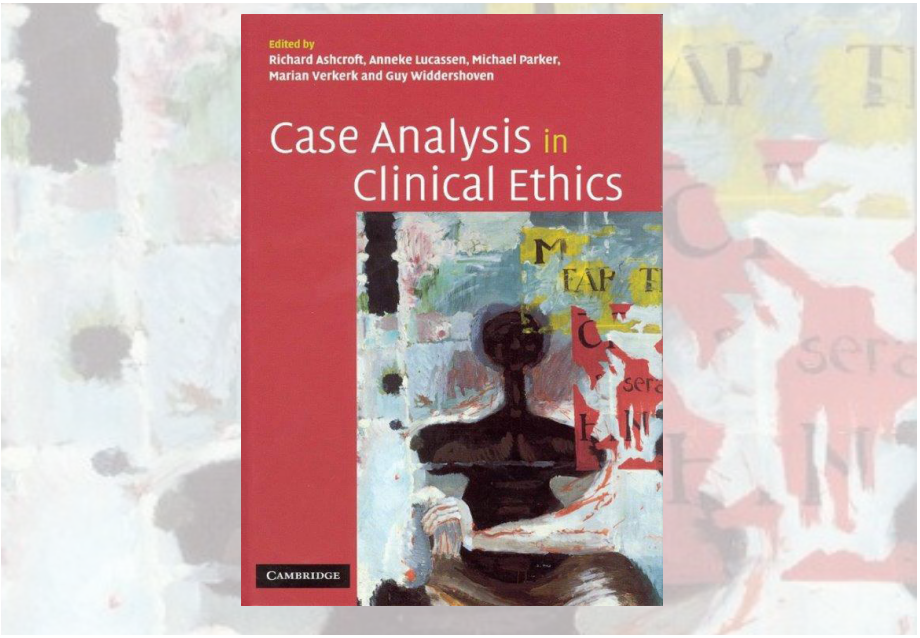


FIGURE 6 EARLY COLLABORATION WITH GRONINGEN ACADEMICS

Whether breach of confidentiality for genetic reasons was an appropriate clinical action in some circumstances was a hot topic for debate as genetic testing took off in clinical practice and it soon became clear that real cases in practice were raising these questions. In 2001, the Wellcome Trust funded a symposium to look at these issues and it became apparent that there was an unmet need for a regular forum for their discussion.

Together with a philosopher and medical ethicist in Oxford -Prof M Parker- and others, I established the UK Genethics Forum[7], a forum that meets 3 times per year at national venues to facilitate multidisciplinary discussion of the ethical and legal issues in real cases arising in practice. This forum is effectively the ethics research laboratory of clinical genomics and has been extremely productive over the years. Its outputs have included national guidelines[8], advice to influential national bodies[9], new research programmes and some 40 or so peer reviewed publications.

Case scenario 1 is a typical (if composite rather than actual) case brought to this genethics forum, and illustrates how clinicians can find it difficult to balance their duties to take consent and confidentiality seriously with alerting others to possible risks they might be at.

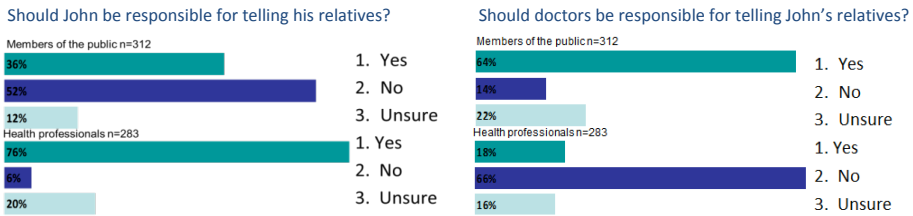
[7] www.genethicsclub.org; 40th meeting to be held at the Wellcome Trust in July 2015
[8] A Lucassen, Tara Clancy, Jonathan Montgomery, Angus Clarke, Alison Hall, Alan Fryer Angela Fenwick, Michael Parker: Genetic testing of children. BSHG guidelines 2010 http://www.bshg.org.uk/GTOC_Booklet_Final_new.pdf
[9] Human Genetics commission, Human Fertilisation and embryology working parties, Nuffield Council of Bioethics, Genomics England Ethics advisory committee, for example

Case scenario 1

Inherited bowel cancer

John is diagnosed with a bowel cancer at the age of 30. Immunohistochemistry of his tumour shows loss of expression of the gene hMSH2 and a gene test subsequently confirms an inherited mutation in this gene. John's father died in his 40s and although he was estranged from the family subsequent enquiry shows that he died from colorectal cancer. The faulty gene (MSH2 mutation) causes a roughly 80% chance (in a lifetime) of bowel cancer. There is evidence that regular screening may be able to catch a cancer in its early stages thus making it easier to treat. The mutation also confers (lower) risks of other cancers, and in women it confers a high risk of womb cancer. John has 4 siblings, 11 nephews and nieces, 10 aunts and uncles; 23 cousins, and thinking about these family members illustrates how genetic information is at the same time individual and familial.

Most people presented with this scenario believe that John's relations have some interest in knowing about John's result because they too might benefit from knowing whether they share the inheritance and may not otherwise find out until they present with a late stage cancer. However when we asked health care professionals and members of the public who they thought should be responsible for this dissemination, we see an interesting difference. Both groups thought the other, an interesting finding for clinical practice as it suggests that communication may be less likely to



Results from public consulation (2013-2014)

take place if both patient and health professional think it is the other's responsibility (see histograms above). This suggests there are practical gaps that need addressing in when and how relatives are appropriately contacted and informed of their potential risk. What is interesting is that health care professionals often said that they were prevented from doing so by ethical reasons or codes of practice, but on closer questioning usually decided that the reasons were more practical; they would not have the time or resources to do so. Clear discussions between patients and health professionals at the time of testing, about how and when their relatives might be contacted, can facilitate appropriate and timely familial investigations.

A joint account approach to genetics/ genomics

Over the last two decades more and more genetic tests have entered clinical practice, and more examples have arisen where knowing about an inherited predisposition might allow people to avail themselves of interventions or treatments that improve the morbidity and mortality of the resultant disease.

The dogma of non-directive counselling that genetics had eschewed in the days where genetic testing was mainly for reproductive risks or untreatable neurodegenerative conditions began to shift. What about the relatives of someone found- sometimes purely by accident- to have a predisposition to heart rhythm disturbances and sudden cardiac death? Should they be regarded more like contact tracing in infectious diseases perhaps? Were the prevailing views about consent and confidentiality in medical practice even applicable in some clinical genetic cases? Parker and I went on to suggest that genetics or genomics might sometimes be viewed through a different lens; one where genetic information is like a joint bank account. We suggested that genetic information discovered in one person should be available to other account holders (close relatives who may also have inherited the same genetic predisposition) unless there were good reasons to do otherwise. If familial inheritance is like a joint account then discovering that inheritance in one person might allow family members to access that information in carefully controlled ways[10].

Most professional bodies governing medical practice suggest that confidentiality is very important and can only be breached if one can prove that doing so will prevent a serious harm. We proposed reversing the emphasis: Where an inheritance was potentially relevant to relatives, one should consider whether disclosure might cause harm to relatives, not whether an individual would be harmed by non-disclosure[11]. An important element of the joint account is that it is not always necessary to breach individual confidence. Rather than identify the proband in whom the inheritance was first identified, John in case scenario 1, it will often be possible to say "there is an inherited tendency to bowel cancer running in your family, would you like to know about genetic tests that will tell you about your risk?"

For many families all this talk about consent and confidentiality is not an issue. One of the main reasons many people come forward for genetic testing is to help their family members. These patients can be bemused by the apparent confidentiality and consent hurdles health practitioners see that prevent them from sharing test results more widely. Most patients attending a clinical genetic service will have some awareness that the service is about families. The first thing a clinical geneticist does is to draw a family tree and take details of the state of health of relatives. Discussions about communication with relatives can be easier than if an inheritance is discovered incidentally (or accidentally); or as genomic technologies are offered routinely regardless of family history. Expectations might be different if a genetic test is done routinely in surgical outpatients without making it clear at the time of testing that the result may have familial implications; that the mutation is relevant to the relation of my title.

[10] M. Parker and A.M. Lucassen. Genetic Information: a joint account? BMJ 2004 329 165-167
[11] A.M. Lucassen and Parker M Confidentiality and serious harm in genetics –preserving the confidentiality of one patient and preventing harm to relatives EJ Hum Genet 2004 Feb;12(2):93-7 and M. Parker and A.M. Lucassen. Concern for families and individuals in clinical genetics J Med ethics 2003, 29 70-73

New technologies are changing genetic practice

Returning to the phenomenal increase in speed and attendant reduction in cost of genetic sequencing technologies with which I started, I want to look at how these changes are affecting genetic practice. Developments in genomic technologies have changed the nature of genetic testing from a focused, relatively narrow inquiry to broader large scale searches, generating large amounts of data and increasing numbers of genetic diagnoses. A fishing analogy illustrates this change in approach. A genetic test targeted at a particular condition is like fishing with a rod and line for a specific fish, not any fish. New genomic technologies examine the whole genome for abnormalities, which is like trawling, where a wide net indiscriminately catches all the fish in its path as illustrated in figure 7.

However, this increased efficiency and decreased cost brings potential problems. What if an entirely unexpected finding is made? There may be no family history to suggest this could be picked up in the genomic net, but it still needs to be dealt with once found. Or can we throw it back into the ocean if a patient explicitly says at the beginning of the process that they would not want to know?

Unexpected, incidental or secondary findings are those that are unrelated to the clinical reason for doing the test[12]. They are by no means new and have been well described in other areas of medicine: for example, the high cholesterol noted when checking liver function, or a lung tumour when investigating back pain. Like with other investigations, the greater the sensitivity of the technique, the higher the chances of finding something unrelated to what you are looking for. The difference for genomics is that an incidental finding may also be relevant for family members, raising joint account questions again, and that any treatments or interventions may not be relevant for many years[13]. This is particularly so where testing is done at, or before, birth so that the person to whom it pertains will not have the capacity to understand what has been found for many years. Case scenario 2 illustrates some of these tensions.

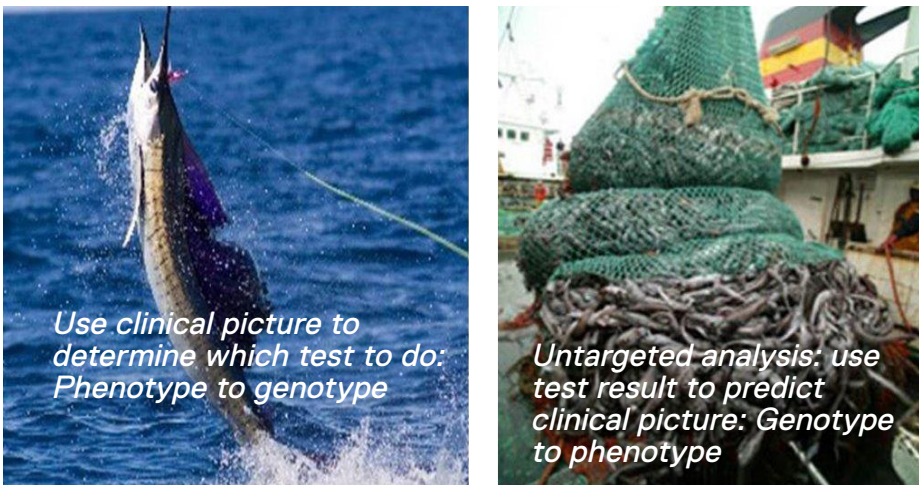


Figure 7 Fishing analogy to illustrate shift from single gene (targeted) testing to whole genome technologies

[12] Shkedi-Rafid S. Dheensa S, Crawford G, Fenwick A, and Lucassen AM. (2014) Defining and managing incidental findings in genetic and genomic practice. J Med Genet Nov;51(11):715-723
[13] Lucassen A, Hall A. Consent and confidentiality in clinical genetic practice: guidance on genetic testing and sharing genetic information. Clin Med. 2012 Feb;12(1):5-6.

Case scenario 2

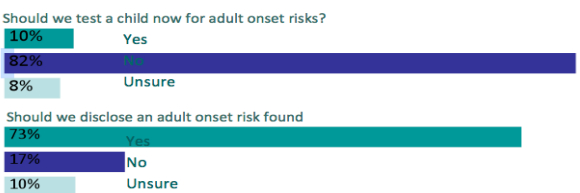
Genetic testing of children that predicts adult onset disease

Version 1: David has just learnt he is a BRCA1 carrier having inherited the breast ovarian cancer predisposing gene mutation from his mother. He has a daughter aged 2 and a son aged 4. He requests testing of both children for the BRCA1 mutation as he would like to know what he has passed on to his children, and the sooner he knows, the better he will be prepared.
Version 2: Chloe aged 2 has developmental delay and subtle dysmorphic features. Genomic testing finds no explanation for her problems but does find a deletion encompassing part of the BRCA1 gene. This means she is likely to develop breast cancer as an adult.

In both cases there are no early checks or treatments that would be helpful during childhood. Screening or risk reducing surgery would not be advised for another two to three decades. The chance of any of the children developing cancer as a result of these genetic findings in childhood is as good as zero percent.

Many international guidelines have been written on predictive genetic testing of children and all conclude that unless there are proven medical interventions that would alter the outcome of the disease in question, and the disease is highly unlikely to manifest in childhood, then testing is best delayed until such time that the child can decide for herself whether or not to be tested.

For version 1 there is general agreement that David's request should be deferred for now, whilst for version 2 the opposite applies. Compare the two results taken from a panel of 580 people questioned using the above two examples[14]. The difference is that in version 1 there is a request for testing to be made that cannot be justified as in the children's best interest now. In version 2, the result already exists and the question about whether to keep it hidden from the parents until Chloe is an adult seems very different[15,16]. When our research questioned health professionals and patients about this they gave a range of reasons: (a) "not fair if the doctor knows something serious about my child and doesn't tell me" [patient] (b) "our record keeping systems aren't good enough to be sure we won't lose this result, or that we'll have systems in place to call her up at the right time" [doctor] and (c) Chloe may have inherited the deletion from her mother who may not know she is at risk of young onset breast cancer and might benefit from screening now. These results, and others, highlighted the conceptual difference between actively looking for something that would be relevant in years to come and accidentally finding it. These are issues that will need further research and thought as genetics and genomics becomes a routine part of health care. A study in Boston[17] is currently sequencing the entire genome of about 240 babies at birth and comparing their lives and medical care with standard new-born screening and follow-up. It will be interesting to see how future predictions are incorporated in the lives of these babies.

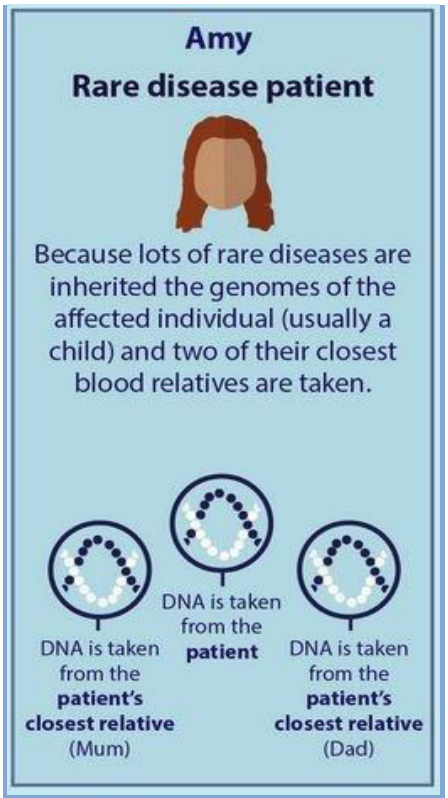


[14] Shkedi-Rafid S, Fenwick A, Dheensa S, Lucassen AM. Genetic testing of children for adult-onset conditions: opinions of the UK adult population and implications for clinical practice. Eur J Hum Genet. 2014 Nov 5. doi: 10.1038/ejhg.2014.221. and ongoing research
[15] Lucassen AM. Widdershoven G, Metselaar S, Fenwick A, Parker M. Genetic testing of children: the need for a family perspective. Am J Bioeth. 2014 Mar;14(3):26-8. doi: 10.1080/15265161.2013.879950.
[16] Lucassen A, Fenwick A. Testing children for adult onset conditions: the importance of contextual clinical judgement. J Med Ethics. 2012 Sep;38(9):531-2.
[17] http://www.brighamandwomens.org/about_bwh/publicaffairs/news/pressreleases/PressRelease.aspx?PageID=1547

The Hundred thousand genome project in the UK

In the UK, new genomic technologies have been received enthusiastically by government. In Dec 2013 the health minister said "We could be the first country in the world where everyone's genome is sequenced at birth and we use it to give people the most profoundly detailed diagnosis of what they need to do to stay healthy" indicating great faith in the power of the genome to predict treatable conditions accurately. In the short term however, the UK has focussed on applying whole genome sequencing to patients referred to the health service, focussing on two groups initially - those with rare disease and those with certain types of cancer. A hundred million pounds sterling has been dedicated to providing 100,000 whole genome sequences. This equates to a neat £1000 per genome, a sum that will pay for the costs of delivering the sequence, but is not sufficient to cover other costs to the health service such as Chloe's mother's referral for surveillance, possible risk reducing surgeries and referral of her and possible siblings/ aunts for similar interventions.

Whilst the 100,000 genome project aims primarily to improve the diagnostic rate in certain disease groups, kick start the genomics industry and provide a legacy for the National Health Service, it provides a fantastic opportunity to investigate how some of my mutation-to-relation themes are realised. Each person taking part has the right to choose whether a list of additional (incidental) findings are also searched for in the whole genome sequence. The list currently includes mainly cancer predisposition syndromes (such as in case scenarios 1 and 2) but can be updated throughout the course of the project so that patients may receive feedback about unexpected findings at any stage. Furthermore, the rare diseases patients will be offered genome testing together with their parents. Such trio testing is to aid interpretation of any findings but means that parents of patients will also be offered incidental findings as well as some results only as a couple and not as individuals[18]. See figure 8.



Trio testing
Person with rare disease both parents are required to help interpret the results:

1. Results that explains disease
2. Additional 'looked for' findings
   a. Cancer presdispositions (but may change).
   b. Risk for future pregnancies. Results will be given as couple results, individual carrier status will not be disclosed.

Figure 8
Incidental findings and couple testing in trios

[18] http://www.genomicsengland.co.uk

Mutation to relation research

What has fascinated me over the last 2 decades is combining three very different skills sets: my scientific knowledge from the laboratory, my experience in the clinic and my ethical and legal expertise. Whilst this perhaps makes me a "Jack of all trades and master of none" it does put me in a rare interdisciplinary position allowing novel insights into areas that trade masters do not have. My aim, and that of my research group, is to cast more light on genomics now that the bottleneck has shifted from cost/ technology limitations to interpretation of the output of ever cheaper technologies. The effective use of genomics in clinical practice cannot simply be realized by delivering ever cheaper technology. High risk, highly penetrant genes are easy to interpret in the context of a family history of disease, but 'personalising' a genome output remains more difficult than commonly perceived. We have interesting research at this interface which complements the Groningen group - led by Prof Van Langen - well. The Bijtel position will facilitate synergism between the two groups in order to maximise these huge leaps in technology into intelligent use.

Acknowledgements and personal note

I would like to thank the Rijksuniversiteit Groningen and the Universitair Medisch Centrum Groningen, and its Raad van Bestuur for naming me the sixth Johanna H. Bijtel Chair holder. It is a great honour for me.

Some ten years ago, I emailed Dr Irene van Langen, then still in Amsterdam, about a genetic test her department was offering that wasn't yet available in the UK. In her reply she surmised from my name that I must have 'nederlandse wortels' [Dutch roots]. She is right, but in the meantime I have spent some 45 years living, studying, practising medicine, and researching in the UK so that above the ground my roots are not always obvious. Like many an expat, I have firmly held on to my Dutch identity, refusing to be considered British, despite loving my life in Britain. This opportunity to nurture my Dutch roots through the Bijtel chair is all the more welcome because it is combined with working at a prestigious university medical centre, with colleagues that have each and everyone been friendly and welcoming, and collaborating with a research group whose interests are closely aligned with mine. Irene encouraged me to apply, has applied her cheerful 'can-do' skills along the way and has in a short space of time become a friend as well as colleague.

Whilst presenting this inaugural lecture, I lodged in a hotel that overlooked my maternal grandmother's birthplace over 100 years ago. Her house still stands, and the cobbles I walked over were probably the same ones she did. I barely remember her, meeting her as a small child when she already had significant dementia. But she passed on her love of studying and her belief that women were academically every bit as capable as men to my mother, who in turn passed that on to me. And so it feels absolutely right that I am here in Groningen in a position that also serves as an academic role model to female students. Thank you all of you, colleagues, friends and family here today, your support means the world to me, and thank you to my parents Emmie Reijnders and Jaap Lucassen who managed to attend despite infirmities, as always my staunch supporters in academic ventures.

Anneke Lucassen, MD PhD is Professor of Clinical Genetics at the University of Southampton and a Consultant Clinical Geneticist at the Wessex Clinical Genetics Service. Over the past 25 years she has carved an interdisciplinary niche combining her laboratory and clinical experiences in order to focus on, and propose practical solutions to, the ethical and legal issues arising from developments in genetics and genomics.

Anneke completed her medical studies at the University of Newcastle upon Tyne UK and did her higher medical training at Oxford Radcliffe Hospitals. She went on to do a DPhil in the molecular genetics of multifactorial diseases followed by specialist training in Clinical Genetics at Oxford. She was appointed as a consultant in 1997 and has been in post at the University of Southampton since 2000.

That she plays a key role in combining laboratory, clinical and ethico-legal expertise to effect improved delivery of services to patients and families is reflected by appointments to the UK's Ethics and Governance Council UK Biobank (-2009); Human Genetics Commission (-2012); Nuffield Council of Bioethics (2009-); Ethics Advisory Committee Genomics England (2014-) chair of the British Society of Genetic Medicine's Ethics and Policy committee (2014-). She has co-run the UK GenEthics forum since 2001 and chairs her hospital's clinical ethics committee.

Her research group (www.soton.ac.uk/cels) examines several aspects of developments in genetic medicine, including the ethical issues around incidental findings from new genomic technologies; tensions between personalised and familial medicine; predictive testing of children for adult onset conditions; and new duties of care created by whole genome approaches.

She is delighted to be awarded the Bijtel professorship and looks forward to learning from, and collaborating with, esteemed colleagues in Groningen.

rijksuniversiteit groningen

umcg