



HOUSE OF LORDS

Science and Technology Select Committee

Corrected oral evidence: Ageing: Science, Technology and Healthy Living

Tuesday 22 October 2019

11.35 am

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Members present: Lord Patel (The Chair); Lord Borwick; Lord Browne of Ladyton; Lord Hollick; Lord Kakkar; Lord Mair; Baroness Rock; Viscount Ridley; Baroness Sheehan; Baroness Walmsley; (Professor Janet Lord, Special Adviser to the Committee).

Evidence Session No. 4

Heard in Public

Questions 28 - 34

Witnesses

Professor Graham Kemp, Professor of Metabolic and Physiological Imaging, Liverpool University; Dr Riccardo Marioni, Centre for Genomic and Experimental Medicine, Edinburgh University.

USE OF THE TRANSCRIPT

1. This is a corrected transcript of evidence taken in public and webcast on www.parliamentlive.tv.

Examination of witnesses

Professor Graham Kemp and Dr Riccardo Marioni.

Q28 **The Chair:** Good afternoon or good morning—it is just about the afternoon, gentlemen. Thank you for coming in. You have been listening to the previous session, so you are well versed in how we progress. We are back on the broadcast live stream. If you introduce yourselves, we can get you on the record. Then if you want to make a quick comment, please do so, otherwise we will proceed to the questions.

Professor Graham Kemp: Good morning. I am professor of metabolic and physiological imaging at the University of Liverpool. By original training I am a clinical medic; a chemical pathologist, in fact. For a long while, I have worked largely in imaging-based research, so another thing that I do at Liverpool is to direct the MR imaging centre, which is a research facility used for a variety of research purposes.

Dr Riccardo Marioni: Good morning. I am a senior group leader at the University of Edinburgh in the Centre for Genomic and Experimental Medicine. My background was initially in maths and stats, and then I moved into epidemiology. Much of my work at the moment focuses on big datasets, so I am combining genetic, epigenetic and other types of data on health outcomes and ageing outcomes, such as Alzheimer's disease.

Q29 **The Chair:** Thank you very much. I start with a question about biomarkers. Can you define what a biomarker is and then tell us how biomarkers can help to identify an ageing process?

Professor Graham Kemp: A biomarker is really anything you can measure that reports on some underlying biological process. It might be a chemical that you measure or a gene whose product you can measure. It might also be some piece of a function that you can measure. It is related in some way to a biological process of interest. That is a perfectly general situation.

In the example of ageing, you are trying to get around the fact that although ageing is inherently time bound—a clock-driven activity that happens at different rates in different organs and individuals, which interact in quite complicated ways—you are looking for ways of reporting on the ageing process as distinct from disease, ideally, in the organs of interest. You are essentially looking at the whole picture, from intracellular mechanisms to genes, epigenetic mechanisms and so forth, as well as the interactions of cells at organ level, the function of the whole body and that of the whole person.

Biomarkers can work at a number of levels. They have causal relationships that are quite complicated. We are interested in knowing how those relate to each other and to the underlying biology, but also to the outcomes of interest in ageing. Biomarkers have a particular relevance to the ageing process, as distinct from disease.

Dr Riccardo Marioni: In the context of today's discussion, I would merely add that a biomarker would be something biological that we can measure, say from blood, saliva or other tissue types, that can be used to predict disease outcome or a trait. Disease outcomes might be something like type 2 diabetes or Alzheimer's disease. A trait, as touched on in the last session, might be biological ageing or trying to predict, perhaps more forensically, something like chronological age—that sort of thing. Excuse me.

The Chair: Please help yourselves to water.

Professor Graham Kemp: I am not strong enough to open the bottle

The Chair: Is that related to ageing at all?

Professor Graham Kemp: I guess so.

The Chair: Would you like a lady to open it? I thought that the power of gripping was related to ageing, no?

Professor Graham Kemp: It certainly is.

Dr Riccardo Marioni: And to cognitive ability. The other things to consider with biomarkers is that we would ideally want them to be inexpensive. If we are talking at population levels, we would want them to be scalable, minimally invasive or non-invasive if possible. It is also important to have something that can be easily implemented and translated, such that healthcare professionals, nurses and doctors can implement it, understand it and communicate it.

The Chair: Does a biomarker always have to be something that you can measure in blood, saliva, urine or whatever, or are there physical biomarkers like the one we just demonstrated on the power of grip? It is a serious question.

Professor Graham Kemp: They come in a variety of forms. Tests of function are biomarkers for the ageing process, as they are for various disease processes. There is a point about convenience and logistics here. It is extremely convenient if you can find something one can measure in a blood sample. In my original background of chemical pathology, that is the classic situation: you take a sample of blood and spin it down, then send the plasma to where the assays are carried out if you cannot do them yourselves. You can freeze them and come back to them; the biobank is a good example of this. If that works, it is an ideal situation.

I do a lot of MR imaging, which is really the opposite situation. The MR machine is highly non-portable. People have to come to it, and it is quite expensive. That is the opposite end in terms of convenience and logistics. You have to understand the biology, know the constraints on the purpose for which you want the biomarkers to be used, and search for the most convenient one. Ideally, it is a blood sample or similar; blood is essentially the only tissue that you can sample from people without seeking special permissions, or without them regarding it as something slightly more than they were expecting when they signed up to the research.

Dr Riccardo Marioni: Your point is quite right. If we are looking for a biomarker of, say, COPD—perhaps lung function or disease—it would involve forced expiratory volume by blowing into a peak-flow tube, or that sort of thing. It need not be from a blood sample. There are other ways to measure it, and that one is clinically used. A blood-based one might be HbA1C or blood glucose for diabetes.

The Chair: I do not want to prolong this too much, but would you advise an average person by saying, “There are things that can test whether you are ageing or not”? In the previous evidence session, we heard about the loss of skeletal muscle et cetera, which gives the power in things like your grip. It might be walking, measured over a given distance, but people can do that themselves: “What is my grip like? I know that it would be ideal if I could grip this cup. Then we can measure the power of my grip”. Is there such a biomarker?

Professor Graham Kemp: Grip is a very powerful predictive biomarker of many aspects of ageing, almost certainly because although it is a simple enough manoeuvre to carry out, it involves a number of things. It involves the cerebral instruction to grip the instrument and it involves the muscles, the bones, the joints and ligaments. To some extent, it involves the ability of the muscle to generate force from the metabolic energy supplied. It is quite high-level in many ways but very easy to do.

That is important in a biomarker; all those things are important. We understand the underlying physiology and what is needed to give a high or low result. What we do not know, without doing specific research, is how to quantify its predictive value for a healthy lifespan and for other aspects of social or physical function. You can do that only by doing the work, and large cohort studies are needed. From that, you can get graphs that relate to things of interest to the grip strength.

The Chair: But simple technology might be developed that measures just the power of the grip, crude though it might be.

Professor Graham Kemp: The technology to measure the power of the grip is absolutely straightforward. Interpreting it correctly is more difficult, and that requires research work of the kind that is going on. What is needed is not a mystery, but how to translate that into a number for the individual doing their own grip for their own interest, for the insight it gives them into their own prospects of a long health span, is quite difficult.

It is not that difficult, but it requires the research work underpinning it. Like personalised medicine, it also depends on a number of the other features of that individual: chronological age, sex and the presence or absence of other diseases. It is the interpretation of the number that is quite difficult.

Q30 **Baroness Rock:** That leads me on to my question on reliable biomarkers.

We have just seen the physical and cognitive capabilities coming together very nicely on the grip. I will now go away and practice my grip a bit

more. How do reliable biomarkers determine how well or how poorly an individual is ageing? Are these biomarkers direct or indirect measures of ageing, and what makes a good biomarker of ageing? Also, we have touched on this, but what are the difficulties in establishing robust biomarkers?

Dr Riccardo Marioni: It is important to highlight the difference between probabilistic and deterministic, if we are measuring a biomarker. Does it increase my chances, or mean that I will get a disease or disorder? Predominantly, we are looking at probabilistic scenarios, so will it increase or decrease your risk?

At population level, that is quite hard to communicate. It is well established that smoking is bad for your health, yet anecdotally some often say: "My grandmother smoked 40 a day, had a sherry before lunch and lived to be 100, my grandfather didn't smoke at all, et cetera". It is about trying to balance. It is probabilistic. If everyone in the UK reduced their BMI by 1 kilogram per square metre, that would have a huge knock-on effect on health. It might not help any of us here individually, but it would help the population. That is important.

In terms of what makes a good biomarker, the last thing we want to do is come up with lots of false positives or false negatives—telling people that they are going to get disease X or disease Y, or that they are fine, and they then go on to develop or not develop something. We need biomarkers of similar accuracy to those that are currently being used. In the genetic screening for breast cancer, for example, are we happy with those levels of probability?

Professor Graham Kemp: It might be worth explaining how we went about trying to define some reliable biomarkers of musculoskeletal ageing, and the difficulty we experienced with that.

Another thing I am part of is the MRC and Versus Arthritis-funded centre for integrated research into musculoskeletal ageing, a partnership between Newcastle, Sheffield and Liverpool. It is one of two similarly named research centres; Professor Lord, your specialist adviser here, directs the Centre for Musculoskeletal Ageing Research. In fact, we work quite closely together but have parallel approaches. In CIMA, as we call our centre, recognising its importance we set out to give this a work package of its own, exactly to determine, identify, and if necessary develop, reliable markers of musculoskeletal ageing.

We discovered that the literature was not developed enough to allow us to make much progress by systematic review. There were a lot of areas where the data simply was not there. Like others in similar situations, we convened a meeting of experts in 2016, gave them subject areas in the various tissues of the musculoskeletal system—tendon, cartilage, bone and muscle, largely, and their interactions—and gave them the brief: what are the reliable, sensitive, specific biomarkers of ageing?

It was extremely difficult for them, and us as the working group in charge, to distinguish markers of age-related disease from the underlying ageing process, particularly with cartilage; there is an enormous amount

of work assessing the state of cartilage in the development of osteoarthritis, driven by academic research and by drug-company imperatives, yet very little on the ageing of cartilage.

We published a large review a couple of years ago in *Age and Ageing*, and our recommendations were that bone turnover is relatively straightforwardly measured by the things that we already knew that it did, because there has been a lot of work on osteoporosis. Osteoporosis is not ageing, it is a disease of ageing, but a lot of the work that has underpinned that enables us to know that. Bone turnover is one of those things that can be assessed quite straightforwardly on blood samples.

There is really nothing to a cartilage, and nothing really for tendons, despite the obvious importance of tendons in delivering the force which the muscles generate for the task the brain wants them to do. Sarcopenia—muscle failing in ageing—which a previous witness, Professor Sayer, is an expert on, is again not ageing itself but a disease of ageing, although the relationship is too close to separate. We found that situation quite unsatisfactory.

The other category of biomarker is the higher-order functional biomarker. A number of toolkits were published to assess the ability to perform tasks with dexterity and at a certain rate. Those functional measures obviously require the physical presence of the individual, but they do not have to go anywhere special to do it.

So those markers exist. But the whole process was quite illustrative, to us anyway, of the difficulties in finding exactly the kind of reliable biomarker that you are asking about. What is lacking on the whole is not concepts or techniques, it is the volume of work in ageing but not disease-group populations.

Dr Riccardo Marioni: Also problematic in the cognitive-ageing area is the heterogeneity around dementia. Specifically, the gold-standard diagnosis is based on post-mortem pathology, so we are trying to think of proxy markers for that during the 20 or 30 years prior to death. We know that the pathology—the plaques and tangles of proteins—that is part of the gold-standard diagnosis starts to build up in the brain from our 40s onwards, so for late-onset Alzheimer's disease there could be a 20, 25 year long disease latency period prior to diagnosis.

Typically, we also tend to see mixtures—Alzheimer's disease mixed in with vascular dementia. It is not a clean phenotype. If we can find biomarkers from the 40s onwards, that might be predictive of diagnosis later. Then again, as with the probabilistic/deterministic thing, we see participants in our studies who have levels of pathology that would be clinically diagnosed as their having Alzheimer's disease based on their brain pathology, but there is no impairment in memory during life. It is quite a difficult phenotype to work with.

Q31 Baroness Sheehan: I want to ask about the current potential use for biomarkers of ageing. How are they currently used within the NHS? If they are not, what is the potential for their use in the future?

Secondly, should biomarkers of ageing be used more routinely for the annual assessment of older adults, and if so, which biomarkers would be most important to assess?

Lastly, what would be the challenges and considerations in using biomarkers as part of a personalised approach to medicine?

Dr Riccardo Marioni: I will take your last point first. We have already highlighted the predictive accuracy of a biomarker. If it is to be included in a personalised medicine set-up, it needs to be predictive to an extent that we are happy with, so equivalent to the likes of troponin for heart attacks, and glucose and HbA1c for diabetes. Again, we do not want to be telling people that they are at high risk of something if they are not, or vice versa.

As to whether biomarkers of ageing should be screened for annually, it depends on the subtleties of, say, a biomarker of ageing as a general global biomarker, or a biomarker of risk of stroke, which might be cholesterol being measured annually or every two or three years. If we are talking about a global index of ageing, it was touched on in the previous session that telomere length is the most established measure that goes with chronological ageing, but there are now more precise measures based on methylation that can estimate an individual's age to within a couple of years just from a blood sample. On average, we can get quite an accurate prediction.

Baroness Sheehan: Are either of the two biomarkers that you have mentioned ready for use routinely within the NHS?

Dr Riccardo Marioni: No, I do not think so.

Professor Graham Kemp: On that point, it is quite a big deal to take a thing into the clinic as a predictive test, certainly as an annual test. Generally the concept of an annual check-up is not favoured in the NHS. Maybe it should be; there is an argument for more surveillance and less reaction.

The issues around screening are well understood. In effect, you would be screening for accelerated ageing, and like any screening test you need to ask exactly what question you are asking, as has already been mentioned. What action follows from it? What are you going to do differently as a result of having that value in someone who is not complaining of anything, who does not have symptoms or signs?

The normal logic of screening applied to biomarkers of ageing as an annual check-up tool is rather unfavourable at the moment. That might change if they became really very precise—the point about precision is extremely important—and with no risk of significant enough false negatives. They would be sensitive enough that it was worth doing. False positives would worry people unnecessarily about their ageing process when you are making only one measurement, which has errors and properties of its own, of one aspect, albeit an underlying and important aspect of the biology.

The practicalities of NHS clinics are also an important factor here. Professor Sayer, your earlier witness, recently published a study of the feasibility of assessing sarcopenia in the normal geriatric clinic. The result, as you might expect, is that something that can be easily assessed with a couple of self-report questions can be done, but it is quite a big deal to measure muscle strength, and a bigger deal to measure muscle mass with some kind of imaging technique.

Many biomarkers would be perfectly good for many purposes—for example, for research and for monitoring the health of populations—but would not be logistically suitable for an individual patient in a clinic. I find it quite difficult to imagine a situation where we would be doing that. The importance of biomarkers is other than that; as I said, it is in population health studies.

Dr Riccardo Marioni: But we could make improvements in, say, smoking assessments. That is included in risk scores for whether or not you are going to be put on statins. At the moment, it is done via self-reporting; when you see your GP, they ask, “Are you a smoker? How much do you smoke if you do?” Methylation signatures are different. We could take a saliva sample from everyone here, look at a single methylation marker and tell you with stunningly high accuracy who is a current smoker, who is an ex-smoker and who has never smoked. We can also work out from these methylation signatures how they change over time.

Baroness Sheehan: Let me focus on single markers. If you have an epigenetic clock and you can compare biological age with chronological age—I think the notes mention a clock algorithm called Horvath’s clock, which measures 353 different epigenetic markers—would that be a more useful indicator?

Dr Riccardo Marioni: There are lots of different so-called epigenetic clocks in use. Again, as touched on in the last session, some are trained more specifically to focus on longevity.

In terms of robust associations, most of the clocks thus far are consistently associated with survival. Lots of people have studied them in relation to lots of different health outcomes and diseases, but by far the most consistent finding is that if your methylation age looks older than your chronological age, there is a higher risk of dying than if your methylation age is the same as your chronological age. In future, the field is heading towards building predictors of specific disease outcomes rather than acknowledging that ageing in general is an extremely heterogeneous and difficult process to measure with only a single number. If we can train a predictor of diabetes, stroke or dementia, that may be useful and have clinical utility.

Lord Hollick: Is there any evidence to show that if biomarkers are used to predict the likelihood of some kind of disease or deterioration, when the individual is told about this they change their lifestyle?

Professor Graham Kemp: That is a very large and difficult question. The whole question of behaviour change is huge, and I would not claim to

be an expert in it. There are experts in it, and they say it is obvious that simply explaining this to someone is not enough, and that you can understand the intellectual arguments perfectly well—we probably all recognise this from our own lives—but taking what in cold-blooded terms is the rational approach to it is not easy.

This is usually presented in terms of medical diagnoses. With cardiovascular risk factors, for example, there is long experience and a lot of literature on this. Whether that would be different if raised in terms of ageing, I do not know. These arguments are probably often phrased in terms of lifespan, actually—cardiovascular risk factor arguments between GPs, and discussions between GPs and patients.

Lord Hollick: Does it heighten the fear factor?

Professor Graham Kemp: I do not know. Being told that you are ageing faster sounds quite intimidating to me. People seem to have internalised the idea that bits of them can age faster than other bits—the idea that, “I have the heart of a 50 year-old”, that kind of thing—so although I am well exceeding my scholarly expertise here, that suggests that there is at least scope for a dialogue about this. However, we should not expect this to be easy or straightforward, any more than any other public health-based discussion between doctors and their patients is.

Dr Riccardo Marioni: It is incredibly appealing to have a single number in the sense of, “Your biological age is 65 but your chronological age is 60”. That is easy to communicate to an individual in a lay sense, but only if we can then say, with robust evidence, “If you make these lifestyle changes, there is a chance of pulling it back”. There is no point in terrifying people by saying, “Your chronological age is so much older than your actual age”, if there is nothing to be done.

Viscount Ridley: Professor Kemp, you mentioned that in the UK the NHS is not quite as proactive in screening people as some other medical systems. In America, if you go in with a cold you probably get an MRI scan—I exaggerate, but you get the point. Professor Sir John Bell, in his report on the life sciences industrial strategy, drew attention to the need for the NHS to be more open to innovative diagnostic tests being employed. Can you give an example of another country that has rolled out a biomarker test with respect to ageing that we could copy or learn from?

Professor Graham Kemp: I do not know of one. The issues are statistical and financial. The technical and medical issues are the same everywhere. The phenomenon that you describe, the wide variation in diagnostic testing in general, varies widely among health systems for no reason that has anything to do with cost-benefit analysis in the standard sense. I am not aware of an ageing biomarker, rather than an ageing-related disease biomarker, that has been successfully rolled out.

Lord Browne of Ladyton: This is completely anecdotal but, in my observation of life, people being told that their heart is younger than they are chronologically seems to be a good thing. It makes them feel better

and reinforces good behaviour, in my experience of people, and they are almost always told this by a medical practitioner.

Dr Riccardo Marioni: But what if you have a young heart and actually have bad behaviours? There is a chance that through whatever mechanism—

Lord Browne of Ladyton: That is a possibility, but there is always a chance that being told something good about yourself will reinforce good behaviour, and that is a good thing.

Professor Graham Kemp: I have seen the opposite. I was thinking about telling someone that they had too old a heart.

Lord Browne of Ladyton: That is why I raised it.

Professor Graham Kemp: It is a very good point, but it also possibly suffers from being irrelevant to that person's concerns at the time. In our musculoskeletal ageing context, for example, being told that you have a young heart is not helpful if you are clearly limited by muscle weakness and joint pain. Although it is based in some science, that fact is unlikely to be perceived as relevant. I suspect this; as I say, I am outside my scholarly competence here.

The Chair: But we have heard in evidence that losing muscle mass is a normal process of ageing. The question anyone might ask is: what if you were able to measure the loss of muscle biomass, then turn to them and say, "But you can now stop it, or even reverse it"? People might do whatever you tell them, but the question is whether the biomarker is there to give that information.

Professor Graham Kemp: If what you set out to measure are the muscle-mass biomarkers and you are prepared to take a little trouble over it, those can be measured. The data exists to show what trajectory you are on and whether you are falling at the normal rate or an accelerated rate. Where you started from will obviously depend on fitness and degree of training in all sorts of ways. The population data exists, providing that you select the right population, to plot out your trajectory as an individual—as a citizen and a patient—on such a graph. There are therapies being trialled for this, as we heard earlier. We do not really have definitive or extremely effective therapies so as to say, "To get back on that course, this is what you need to do", but the prescription would probably be for an increase in physical activity.

The Chair: But we do not have effective or definitive therapies for most diseases.

Professor Graham Kemp: Indeed not. We can advise people to make incremental improvements in various aspects of their lives, some of which will involve prescription.

Baroness Walmsley: Is there any consensus about the set of features and factors that, put together, mean that somebody has a chronological age of 60? It sounds as if it might be a little subjective. Has there been work on that, and is there general agreement?

Professor Graham Kemp: I do not think it is subjective so much as very complicated. The functioning human being, however you think of us, is the sum of a lot of working parts, all of them affected by age. We are interested in musculoskeletal ageing, but in focusing on that we do not forget about what we bracket off: the heart and the cardiovascular system, more generally; the respiratory system; balance; memory and perception. All these things have a general downwards trajectory, melancholy though it is to put it in these terms. They go at different rates and interact in different ways, so I would not really attach any importance to the concept of a biological age.

Baroness Walmsley: But if you took even one organ, say the heart, if somebody is told that they have the heart of a 60 year-old but is actually 66, who has decided what the heart of a 60 year-old looks like? Is this an average across the population? Where does it come from?

Professor Graham Kemp: I would not say that to anybody but I could point to the graph that I mentioned to locate someone on it. It might be a graph of muscle mass or function; there are a variety of ways of measuring this. You could say, "When you started out aged 20, you were in the top 5%. Now you are in the bottom 30%". You could make that kind of statistically-based individual assessment. Again, I do not personally think much is gained by trying to phrase that in terms of biological age, even of a particular system.

Q32 **Baroness Walmsley:** I was just thinking that you would have to measure an awful lot of people to be able to do that, which brings me to my question. It is about datasets.

Are large datasets such as the biobank being used to determine and measure biomarkers? Are these datasets collecting the right things to determine the robust biomarkers that Dr Marioni was asking for earlier? What further data, such as biological examples, could be useful for the development and monitoring of these biomarkers?

Dr Riccardo Marioni: The UK Biobank, for example, follows half a million individuals. If we are going to apply novel technologies and new biomarkers, we need to be confident that they are highly predictive to begin with. To run that on half a million people would be very expensive if we were not certain of the performance, so there is a need for mid-size studies.

One that I work with is Generation Scotland, which involves 24,000 people from across Scotland from whom we have blood samples. We have methylation measured on 10,000 participants, which is the largest example of that type of dataset in the world. Through data linkage to electronic health records—GP records, hospital data and prescription data—we are able, after a single blood sample the first time that they come to the clinic, to follow them up through their health records. If some exciting technology is coming out, which might be methylation, we can measure that on 10,000 people. It is still expensive, but it is not a 500,000 person study expense.

There is also still a need for the smaller, really detailed studies that target specific subsets of the population. Another study that I work on is PREVENT Dementia, which involves individuals at a higher risk of developing dementia based on family history and genetics. They are in the 40 to 60 age range. There is bespoke cognitive testing for the specific domains that start to decline with Alzheimer's disease. There are longitudinal brain scans; there is amyloid-PET imaging to measure the plaques and tangles in the brain; there is the collection of CSF.

That is not really feasible on the scale of hundreds of thousands. But if we have blood and CSF from our participants in PREVENT Dementia, and find something in the CSF that we think is useful, can we build a predictor from bloods that proxies that CSF marker? It might explain 70% or 80% of the CSF marker. Then we can roll it out into our bigger studies, like Generation Scotland, and see whether it associates with cognitive outcomes there. If it looks promising, we might then try to obtain funding to roll that out into a biobank.

Professor Graham Kemp: The UK Biobank has its limitations. They are essentially logistical and practical, not so much ethical, but there is no way that CSF can be collected in a cohort of that size. But within those limitations, it is a remarkable resource.

To come back to the point about the portability—let us call it that—of biomarkers, if blood is collected it is available. As you know, a variety of research projects are being done on these stored blood samples. If you make your argument to the biobank organisation, you can get access. That is enormously useful.

Imaging data has now been added to a large sub-cohort, as you will know, and given its logistics some impressive imaging has been done—brain, cardiac and abdominal imaging. Again, that data is available to be linked with a general health outcome questionnaire. It is being interrogated all the time. The list of projects being done on this includes quite a lot in a “healthy ageing” domain.

The one thing that you cannot go back and do is catch some functional test that you did not think of doing at the time. Obviously, that is the problem with cohorts. People who have worked with existing cohorts, some of them very long, have found various ingenious ways around this. In CIMA, we originally intended to set up our own cohorts but did not do so in the end. We could see that it was being done on a larger scale.

Baroness Walmsley: What are the ingenious ways around it?

Professor Graham Kemp: First, finding data that you did not know you had. I put into that category the whole area of machine learning. This is slightly unprofessional, but I think of that as being able to tell you things you did not suspect about a large amount of data that you did not quite know what to do with. Putting together disparate data is something that machine learning approaches make possible.

Dr Riccardo Marioni: On the question of hidden data that you do not know you have, there are initiatives in place, certainly in Scotland through the NHS. There is something called SHARE, which about a

quarter of a million people signed up for. You can opt in online, and if there is routine blood sampling by your GP, for cholesterol or whatever else, if some of that sample remains it can then be stored. Further down the line, you might be recruited to a study, such as of females between 50 and 60 with diabetes. They might wish to recruit you to the study through data linkage to your health records, then go back and analyse those stored blood samples.

Another thing that will be really exciting is the Guthrie card blood spots. This is the heel-prick test that is done on newborn children for a variety of outcomes. There is a moratorium at the moment on their use for research, but we have been given permission by the Scottish Government and the Chief Medical Officer to run a feasibility study on potentially using them for research purposes to see if we can obtain methylation on them. If you have that anchor at birth, you can get genetics and methylation, which might predict childhood diseases and disorders, even those into adulthood. There is potentially a lot of data that could be useful.

The Chair: In a way, what is shared in the Guthrie card is a biobank for blood samples for future analysis.

Baroness Sheehan: What sort of timeframe are we looking at before we can identify biomarkers using data that is already generally available, such as blood tests, electrocardiograms and data from comparable devices?

Dr Riccardo Marioni: From a statistical perspective, the more people we have in our training data set to build and develop these predictors, the more accurate they are going to be. There has been a step change in genetic epidemiology through the release of UK Biobank data. Instead of having cohorts of tens or hundreds of thousands, we are now at half a million plus.

It makes a big difference. If we could train a methylation predictor of smoking, BMI, whatever, in half a million people, it would be incredibly precise compared to what we have now. We may well be able also to develop precise predictors of other specific disease outcomes. I think it is about generating the data, and then taking advantage of the expertise of statisticians and machine-learning specialists who try and generate robust predictors.

Professor Graham Kemp: There are advances all the time in this area. New mechanisms yield new potential markers—the Tableau mixed approaches, the multiple measurements on those stored blood samples, allied again to machine learning, or at least to techniques that can handle data sets of the size that these techniques yield.

This cannot fail to be useful in the generation of biomarkers. Whether there will be some transformational biomarker that is very much better than any of the others in the respects that we have discussed I do not know, but that kind of work is going on on an annual, five-year, 10-year basis. We will know a lot more about biomarkers of healthy ageing in 10 years than we do now.

What we cannot do with those datasets is make measurements that involve the physical presence of the subject at the time. This data is not going to yield that kind of biomarker. Stored ECG data is available for anything that requires some sort of innovation in the acquisition of the data.

Generally, MR methods are an intermediate case, because the MR data that is stored as part of the UK biobank initiative is done very well by contemporary standards. It is available for re-analysis. The analysis is not done once and for all and the results are not set in stone; it is available for re-analysis. That kind of work can be done and is being done, but if there is something which in retrospect you thought you should have done at the time of acquisition, or something was not available in the machines at the time but is five years from now, which will certainly happen, we have missed that opportunity, but we will hopefully still be recruiting to new biobank databases.

Q33 Lord Browne of Ladyton: We are told that the usefulness of biomarkers includes their helpfulness in determining whether interventions are having an impact on the underlying ageing process. For completion, my understanding is that it comes from an American Federation for Aging Research publication in 2016, *The Biomarkers of Ageing*.

So the question is: are there clinical trials that target the ageing process, where biomarkers are being used to determine whether clinical interventions are having an effect on those markers? If so, which particular markers are being selected for testing in those trials?

Professor Graham Kemp: That is certainly the case. One obvious use of a biomarker is as an endpoint in a clinical trial. That is as true of an ageing intervention as it is of the trial of a disease therapy.

A lot of the markers that we have discussed are currently being used in clinical trials. In the musculoskeletal area, in measures related to muscle strength and function, there are several trials going on at the moment in Newcastle-upon-Tyne—interventions in sarcopenia using sarcopenia-related musculoskeletal biomarkers.

Functional measures of posture control, of balance, are used in clinical trials of interventions. I said earlier that cartilage is much studied in the specific area of osteoarthritis, so it is quite difficult in that case to separate ageing trials from osteoarthritis therapy trials. The situation is slightly similar with osteoporosis: lots of trials of therapies for osteoporosis use uncontroversial biomarkers of bone ageing.

There is no single answer to this, but all the biomarkers that we have discussed are being used as endpoints in trials where it is appropriate. There is no inhibition about using them. If they are the right markers for the task they will get used. They might be the primary endpoint, in which case they control the size of the trial, or they might be secondary endpoints. In our own work in Liverpool, we have tried to recognise that in order to understand how various measurements relate to each other, but it is quite difficult to get funding for trials that specifically study that.

So it is very tempting, and within this kind of context justifiable, to use the opportunity of an intervention that you think would do this or that to your primary endpoint to add some secondary endpoints, precisely to understand the complexities of the underlying physiology. That is a trial of treatment effect, of ageing intervention effect, but it is also a mechanistic trial of underlying physiology and biochemistry.

There you might pick a biomarker that is not necessarily a good generic biomarker of the ageing process but will tell you something about what is going on in the liver, for example—the liver is an organ that ages in important ways—or the heart. This is one thing that we try to do with our own intervention work. We do a lot in type 2 diabetes, actually.

So it is not that there is a big issue about using biomarkers of ageing in trials of ageing interventions. If they are there, are feasible and have the right properties, as we discussed earlier—reliable, sensitive, specific and under proper technical control—they will be used. That is true of my area of the field, anyway.

Dr Riccardo Marioni: I would add something about the potential of using biomarkers, if you would still label them as such—things like underlying genetic risk—to recruit individuals into clinical trials by finding subsets of the population at greatest risk based on their underlying genetics, or based on any of these potential biomarkers, dependent on the trial in question. It might be a way to accelerate or expedite clinical trials by selecting those at greatest risk, or where you might expect to see the biggest response.

Professor Graham Kemp: Formally, there would be recruitment criteria, but there is still a use of biomarkers in trials, which is slightly different from what the American statement recommends.

Lord Browne of Ladyton: For clarity, I was not intending to imply that I thought there was an issue about using biomarkers. From my perspective, I am more interested in whether, when it comes to our recommendations, we might want to engage with this issue, and whether you could draw our attention to specific examples of where biomarkers were used to effect in clinical trials so that we could consider whether encouraging more of that would be a good thing or not.

Professor Graham Kemp: Yes, the point is that people should be using the right biomarkers and obviously we should be encouraging them. That was the purpose of the exercise that we went through with our musculoskeletal, or CMAR, toolkit, as we call it. A toolkit is an obvious and attractive metaphor for looking at this intervention and its impact on this tissue, this system: "Here is the right tool for the job". We found that we lacked data and therefore could not make recommendations for quite fundamental aspects of the musculoskeletal system, which is potentially only four tissues working together.

There are general recommendations for ageing biomarkers. Some are in areas where I would not know whether the effective biomarkers are being used in the right trial. Certainly in relation to frailty, locomotion and physical function, we would hope that our recommendations are having

some impact. However, our recommendations also included the recognition that there was not a good marker for this yet, which is also important: that people do not waste time and money on markers that are ineffective.

Focusing on the markers as markers forces attention on all the properties of a good test, a good marker, that we have discussed. A really modern trial design should force those discussions anyway on anyone setting up a trial. The power of a trial depends on the effectiveness of the endpoints in assessing the underlying hypothesis. Trials that are using inappropriate endpoints really should not be happening.

That is not to say that there was no point to our work or the work of this Committee. This is about looking at the data and seeing what the appropriate endpoints are for the particular purpose. I do not think that there are generic ageing endpoints, at least not in my world; you may have a different perspective on that.

Dr Riccardo Marioni: I agree. For the more general, broad biomarkers of ageing, whether it is telomere length or epigenetic clock, currently these are not precise enough for specific anti-ageing trial outcomes. However, they are very interesting secondary or tertiary measures to help inform us of the potential for their use as biomarkers for future studies.

Q34 The Chair: I have two questions. Perhaps you could give brief answers and then we will pack it in. They relate to the question that Lord Hollick asked the last panel, which was about this Government's strategy to extend what they call "healthy ageing" by five years, and the suggestion that it is not the science but the technology that will be more important in driving that improvement.

Also, you were listening to the evidence in the previous session when Professor Faragher mentioned the TAME trial of metformin in the United States suggesting that you could use biomarkers in a clinical trial situation with two cohorts to determine at two individual points whether the intervention was having a desired effect. If that was the case, that it could be used in clinical trials, why can it not be used in general population screening between ages?

Two separate questions, but they are linked.

Professor Graham Kemp: On the population screening issue, it depends on whether the probabilities of properties of the tests stack up—the properties of the population, the deliverability of the test at scale, whether it makes sense as a screening device—and can be decided on the evidence. I do not really have a view on that at the moment, but the bar is set very high, for reasons we have discussed.

I am not sure that this addresses the point, but one general issue about the use of biomarkers in interventional trials, and cohort studies to assess their properties in the healthy ageing population, is that we need to make more frequent measurements. We have relatively sparse sampling over time, I think, for logistical and practical reasons. One aspect of that is

that the biomarkers of healthy ageing are probably better assessed earlier on in age—I think that somebody said this in the first session—before age-related diseases have confused the picture. Somebody needs to be funding studies that involve more intensive sampling of younger populations. That may not address exactly what you asked.

The Chair: It does partly. What about the question about government strategy?

Professor Graham Kemp: There is a funding implication to that, but I had not really thought about that issue until I heard it raised in the earlier session. I am not unhappy with the existing mechanisms for funding work in this area. What was being proposed, I think, was something more radical, on the model of the US NIH. That did not strike me then, and still does not an hour later, as the issue. I am not necessarily committing to this for ever, but that is not the issue: the issue is making funding available for the sort of studies that need to be done, which are not radically different. That is probably all that I have to say on that subject.

The Chair: In several answers, you and witnesses in the previous session made a plea for more funding for ageing research, without actually showing evidence that supporting more ageing research than we already have is going to be beneficial in some way.

Professor Graham Kemp: All I have done is point to areas where the evidence is not yet there. If we want the evidence to be there, money will have to be spent on getting it. That is how I would phrase that, rather than as simply a plea for more funding in the way that consumers of research funding always plead.

Baroness Walmsley: I would like to explore a little something that Dr Marioni said earlier. I was interested in what you said about Scotland, where people having a routine blood test were asked to give their consent to what was not needed for the specific test they came in for being used for research. Was that because it was felt that there was a need for more resource material for research? If so, will the success of that be monitored and evaluated? Perhaps we should be thinking, if it is successful, that we could use it elsewhere in the country.

Dr Riccardo Marioni: I am not the best person to ask that question to. I am not that familiar with the nuts and bolts of the SHARE mechanism. Ultimately, it is trying to expedite medical research.

The Chair: It was started in Dundee.

Baroness Walmsley: But it provides more resource material for research.

The Chair: I had nothing to do with it, I might add. It was started in Dundee by the clinical research department as a way of people voluntarily giving a sample of blood that could be used subsequently as more knowledge develops, to analyse it in the cohort way. Let us say that in a sample of half a million people, there were 20,000 diabetics. They would then have a genetic marker, and a drug could be developed that would

be more efficient for people with those genetic markers. That kind of study might become possible. Hence the use of Guthrie cards, which was not initiated in Dundee, by the way, but is similar.

Thank you very much for coming. It has been most helpful. I do not know whether we solved a lot, but we certainly learned a lot.