

## Ian Sayers Asthma

	<p>What I thought I'd do is I'd just talk a little bit about a particular area that I'm interested in which is focussed on Asthma. The targets split into these sections. I'm going to talk a little bit about asthma and why it's a really complicated disease and why we need new medicines, talk a little bit about asthma as a genetic disease, a little bit about the approaches that we use into map genes and really focus to why UK Biobank is an absolute fabulous opportunity for us in this research area. I will end by talking a bit about where we are going with this type of research.</p>
_00:00:31_	<p>So I'm sure you're all away that asthma is a very big problem. 100 to 150 people worldwide have asthma, that equates to 5.5 million in the UK alone are actually taking medication for asthma, 1.1 million children, 4.3 million adults. And again quite a sobering statistic is that every 17 minutes a child is admitted to hospital in the UK because of their asthma. And also we can think about economic burden for the UK, talking about £1 billion per year to the NHS really focussed on asthma treatment and costs.</p>
_00:01:07_	<p>And again it's important to know that asthma, there's no cure for asthma available and there's only treatment that treat symptoms and manages those symptoms and really we need new medicines for asthma.</p>
_00:01:18_	<p>As I've mentioned asthma is a complicated disease. It presents in different ways. The typical symptoms are wheeze and breathlessness and airway obstruction and it's really quite a horrible disease to be fair. Also airway inflammation so inflammation occurs in the airways and what we've found in previous data is that asthma really is about genetics but also about the environment so there's those two combinations that lead to the development of asthma.</p>
_00:01:49_	<p>Also it's quite important, it makes it a challenge from a genetic point of view, is that asthma is really hydrogenous so different asthma patients present quite differently and we think have quite different underlying mechanisms that drive their disease.</p>
_00:02:03_	<p>So on this slide just to add to some of what I've described about the symptoms and if you look inside the lung of an asthma patient it's incredibly different. So on the left is a normal individual, as you can see this is the airway and this is a cross section of an airway, so the airway tube basically and if you look at the right it's incredibly different. There's excessive inflammation, there's lots of airway obstruction, muscle bundles so essentially it's very different to a normal individual. And we really don't understand in detail how this comes about and we think genetics might be able to understand some of these mechanisms that lead to this structural change in the airways leading to asthma.</p>
_00:02:50_	<p>Don't really worry about the details on this slide but this is a little bit about how asthma is currently managed or treated. So the approach is a stepwise approach. So a person comes to the GP, they get diagnosed with asthma and they give them an inhaler, the first step of treatment and really that medication is increased in a stepwise manner to try and manage that person's asthma and control that persons asthma and keeps stepping up through things reaching ultimately things like oral steroids, high doses and then, when asthma is maintained or controlled it is then stepped down and</p>

	this is the current management of asthma at the moment.
_00:03:27_	What's quite important to say on this slide is that this stepwise management of asthma, once you've started reaching the higher steps there are patients that really don't get any benefit from existing drugs and these are the more severe or refractory asthma subjects which is one of the particular areas that my research is interested in.
_00:03:50_	So I think you'll see there is a need for new medicines, particularly for those severe patients that don't really get good benefit from existing medications and we're talking about 3-10% of patients with asthma have severe asthma. Treating options are limited, even on very high doses of steroids for example and what we think is that severe asthma may have different mechanisms. So part of my research is to try and understand those mechanisms that drive that disease and we think genetics is quite important in that driving so UK Biobank is a fabulous opportunity to start prising out some of those genetic changes.
_00:04:26_	If we think about genetics and how it works, we had a nice talk earlier about risk and predisposition in a way, what's shown on this slide is why asthma is particularly a challenge. So we have diseases that are considered simple diseases even though they're relatively complex things like cystic fibrosis where there's a very big genetic effect and therefore mapping genes is a little bit easier, the problem with diseases such as asthma is there is, like I mentioned earlier, there is a genetic predisposition and then it depend what you see in the environment that double hit then leads to the asthma presentation and those things could be things like smoking, or virus infection in the lungs, air pollution for example and of course allergens and we know that asthma and allergy are related.
_00:05:16_	We put it on this slide earlier, it's a complicated slide but what this relates to is the parcels we talked about earlier, genetic parcels that span the entire genome and for intents and purposes our DNA is a string of letters. We all have our own string of letters that are unique and what is different about those letters is that some of those letters change our genes and change the regulate those genes and these are the things that cause disease ultimately. So shown in the middle of this slide is actually a string of bases or letters and in the middle of the genetic change and this is really what we measure predominantly in our genetic studies, this is the parcel that we measured 800,000 of them across the DNA to see which parcels go with the disease.
_00:06:06_	This is a typical type of design that we use in genetics. So we have people with asthma and we have people that don't have asthma and basically we look at their genes and their genetic changes and see if genetic changes are more common in those people that have asthma compared to those people that don't have asthma. And we do this many many times across the whole resource and this helps us identify genetic changes that might be risk factors for the development of the disease asthma.
_00:06:33_	We've seen one of these plots before, this is the Manhattan Plot, named after New York City of course. And the spike basically tells us that there might be a genetic change in that region that might be important for asthma and so this is the type of thing were hoping to get out of our study actually when we complete and this is an early study in asthma showing that many genes across the whole DNA might be important in asthma and it's very small changes in many different genes that we think

	cause asthma.
_00:07:04_	So now I've taken a little bit of a step back. So I've been involved in a large collection of asthma subjects, patients from across the UK, The Genetics of Asthma Severity and so what we've been doing is recruiting patients predominantly from hospital settings and particularly patients that have severe disease because we think in particular this is a really unmet clinical need and this is where we are at the moment. This picture really shows that we've collected all across the UK and also in Northern Ireland, 16 centres and we've collected around 4,000 subjects and about 3,000 of those people have a moderate to severe disease so the sphere end that I mentioned earlier.
_00:07:49_	So why is UK Biobank really important for our study? It's a fabulous resource, half a million people as have been mentioned before but the key thing for us is the clinical information is really comprehensive and also slowly becoming available as the genetic information. And in particular to my study, using the asthma patients that I've just described that we've collected across the UK, of course UK Biobank has been collected across the UK as well so genetically our patients are very similar to UK Biobank participants.
_00:08:22_	Also what's really important to flag is that within that half a million people of UK Biobank about 60,000 people have asthma so it's a really important opportunity to look at asthma genetics just within UK Biobank as well. And also what's been touch on previously is that genetic changes across our patients and also UK Biobank have been measured in exactly the same way using the same technology which is really important in genetics so that we can now combine all of that resource with our and also UK Biobank.
_00:08:54_	This is how we plan to use UK Biobank data in a case call design that I've mentioned earlier. So where we take people with asthma and without asthma and compare their genetics and this is the strategy we're about to do actually, we're just at this late phase. So where we'll take our moderate to severe asthma patients and we'll compare them to control subjects from UK Biobank, these are people that do not have asthma, do not have allergies and do not have a respiratory disease. And there's rare resources in the world that you can pull the types of numbers that actually you can exclude those common founders in this type of analysis. We're doing this in a discovery setting to identify new genetic differences and then as mentioned again earlier, replication of repeating those types of tests to show that it's a true result, we'll do that also using Biobank samples as well. Again this time asthma patients from Biobank and also controls. Also as part of this study we were very keen and our secondary objective is to compare mild asthma to moderate-severe asthma. As I mentioned mild asthma is generally quite well managed using the current medicines and what we'd really like to see is also is what's different about mild versus severe asthma. And again there's an opportunity in this study to answer those questions from a genetic prospective.
_00:10:12_	So where are we now? We have all of the genetic information and we're finalising some quality checks on that data. From our own study we have about 2,500 asthma patients available for this analysis and we've started using the really rich UK Biobank data and at the moment we have access to 150,000 UK Biobank data sets and what we've found is that when we use our checks to exclude things like respiratory

	disease/allergies we've got about 97,000 people that we can use as controls for our study and also in the main analysis. We've also found that in the 150,000 people that we have data for now, about 18,000 of those individuals have an asthma diagnosis and that again opens up opportunities of how we can delve into asthma and also stratify asthma which is what we're doing at the moment to identify those moderate/severe subjects in that 18,000.
_00:11:10_	So the next stage is, it's important to say is that through the fantastic opportunity of UK Biobank this will actually be the greatest and largest study of moderate to severe asthma in the world. There's no studies that have used these types of numbers before and so there's a really nice opportunity to get something novel and really interesting to really help us understand severe asthma. Again, when we look at mild and moderate asthma and again we're hoping to see potentially something different there. And then also again very large numbers there was a real opportunity to find novel genetic things underlying asthma per say by combining all of our data and UK Biobank data.
_00:11:50_	So what do we hope to get out of this? Really we hope to identify novel genetic risks that basically predispose you develop asthma and in particular, as I've mentioned, try and home in moderate-severe asthma that's really not very well managed with medicines at the moment. And why is this important? It's really important because this gives us a potential opportunity to identify new mechanisms and new things that drive the disease and only by understanding the disease in more detail can we really develop new drug targets and new medicines. So it's fundamentally important.
_00:12:27_	So just come towards the end. So again just to reiterate it's really important to say thank you to all the participants of UK Biobank, it obviously would not have happened without the free time that has been given to this and also our asthma patients that have been recruited across the UK. I'm stood here by myself but of course I have a massive team behind me that are involved in this study, particularly in Nottingham where the research is and Ian as well and also in Leicester and particularly the genetic epidemiology group or analysis group and then the other people listed on these slides are scientists and clinicians that have collected the samples from across the whole of the UK and made this sample... made this study actually viable. And again Asthma UK I want to say a special thanks that funded part of my study.
_00:13:20_	Okay so I'll leave it there for now and I'll open to any questions.
	ENDS 13:32