I have been working in the AMD space a long time, and I want to speak to you about some of the things that Carmen touched upon, that is imaging of drusen and age-related macular degeneration. When we see an eye that comes to us and we look in their fundus you often see patients that have just a few drusen, or those that have a lot more. And the question is always are the patients that have more drusen, are they at greater risk of developing end stage disease? It’s not so simple.

If you look at the – this was a great image I think, this was an electron micrograph from 1987 and this is a patient with AMD, the eye bank and the RPE is peeled over, and what you see here under the RPE layer, this orange is Brook’s membrane, are these drusen. So the drusen look like crystalline structures and they sit right beneath the RPE, this is really fascinating to me, I have never seen a better image of drusen than this one with scanning EM.

Okay, now I’ve been involved in several age-related eye disease studies, I was one of the principal investigators in AREDS 1, and in those trials in order to qualify for a trial you need to have at least some drusen. So drusen are sort of the semiquinone of AMD. And if you didn’t have a drusen, even if you had lost vision in the other eye from a previous AMD event you still couldn’t get in a trial.

Now risk factors for progression of disease include several morphological features including clumping of pigment, the number of large drusen, at least historically, the total drusen area, whether you have geographic atrophy and then obviously how long do you follow the patient for?
One of the things that’s interested me is we’ve got this nomenclature about the size of drusen, and large drusen are fairly important, they are always mentioned in articles and they are supposed to be between 100 and 25 and 249 microns, or 250 microns in size. But one of the things that’s very confounding and very few people really realize it, in fact I didn’t realize it until I dug deep in some of the previous historical papers is this druse, which is 125 microns across is not a large drusen because the way they define it has to do with the minimum diameter, not – or the minimum dimension not the greatest dimension. This is not intuitively obvious, so to me this is just another reason why the, the field is sort of confounded. But when NEI or these publications regarding AREDS all those publications, they talk about large drusen, they are talking about one whose minimum dimension is 125 or greater.

And then there is these severity scales. If you look at a patient with AMD, dry AMD, you can sort of help predict how they might do by looking for certain features and the features are fairly simple, whether they have the other eye being already affected by an event, whether they have pigment abnormalities or whether they have a large druse. So these three things are very important in sort of coming up with a guess as to how much at risk your patient is.

And why are risk models of CMD important? Well, we know as Carmen mentioned we have some pretty nice treatments for wet AMD but they only work if you identify the patient. So if a patient is at high risk, and they don’t notice that they converted to wet, then they are not going to do well. So knowing who is at high risk you are going to see them more often.
Also if you are going to look at strategies that are prophylactic in nature, that is ones that might prevent progression of AMD, in those trials you want to select those subjects that are likely to progress within the time frame you are going to study. So you want high risk patients, so knowing risk is important in that regard. And then finally the patient as well as the family members sort of want to know how likely this individual is to develop end stage disease or lose vision.

Now there is some other severity scales that have been defined, I mentioned the very brief one, or very useful one clinically but the ones that were derived very pedantically were derived from the studies of using trained readers. They were reading drusen using overlaid templates on projected photographs. These were really before the days of digital imaging, and they assessed the different regions and they counted up the number of drusen, of different sizes using these templates and they also measured the total drusen area. But the reproducibility of these measurements really isn’t all that great. They were sort of generally on reader, between readers they generally agreed but not, not really spectacularly. Now we know we can image drusen on OCT and we talk about that drusen seemed to - can change the overlying retinal layer.

This is an image out of the Retinal Physician here, drusen here and you can see that the outer nuclear layer is a little bit thin here. But I’m not sure if that’s because these drusen are actually pushing into the retina, and remember the retina is pretty elastic. Or is it because there’s a problem with nutrition because the drusen are there? I’m not sure it’s mechanical.
And then the other thing that comes to mind really what is a druse? How do we define it now? We know how they look, at least we think we do on color images. But now that we have OCT do you need some OCT reference to really dictate what a drusen is, what a drusen, or what drusen are. So this sort of makes things simpler but also confounds things because there’s not an agreed upon definition.

So one of the things I was interested in and still am is doing quantification of drusen over time, and years ago I went to a Greek island actually on a sabbatical, worked with some colleagues and we made a drusen reading program. And we use that to measure drusen and drusen areas. So essentially it’s an algorithm that can take an image such as this and with interactive controls you can define what you think drusen are and the software helps you and then it comes out with the measurement of total drusen area as well as the individual size of all the drusen in the image. And that’s been published in 2007 and the reason I wanted to do this is if you look at drusen specifically maybe by measuring drusen area for instance over time that might be predictive of risk.

And with respect to how robust is this software, at least between readers there is a very good agreement when you have them read let’s say an image for drusen area, you have a cap of about .86. So we looked at, we were assessing risk in a bunch of subjects that were participating in previous AMD trials including the AREDS trial and there was also a trial called the Prophylactic Treatment of AMD, which I directed and that was a trial where you use laster to make drusen disappear in an effort to try to see if drusen disappearing was a good thing. It turned out that it didn’t really matter very much, didn’t really help. But in any case we had a lot of patients that had drusen and we used
only the untreated eyes in those PTAMD patients, and we looked at these 513 subjects to look at their baseline data with respect to drusen and some other criteria to see what would be the risk factors that would be predictive of which ones got into trouble.

So we looked at ETDRS visual acuity, presence or absence of wet AMD in the fellow eye, the number of drusen of different sizes, follow-up time and the age and so forth. And we looked at the central 1,000 and 3,000 microns. And these are the results. So just bear with me, I’ll just touch upon them. If the fellow eye is affected it’s really an important risk factor. So if you have a patient that the subject eye – excuse me, the fellow eye has already been toasted by wet AMD they are at high risk. If you have pigment that also was a significant factor. But surprisingly the total drusen area, at least at baseline, was not significant. But it appeared to be a situation where they needed to have a certain amount to reach threshold to enter into a risky category. So the idea, at least this is unpublished, but hopefully we’ll get this published, is that more drusen doesn’t necessarily mean more risk, but you need a certain number of drusen in order to have a substantial risk.

Now you can measure drusen area on a color image, but if you measure it on OCT you might actually – and it seems like it’s fairly obvious, you might get quite a different number. And then the whole question, Carmen touched upon drusen volume, well I guess I pose the question if drusen area isn’t so important, if it isn’t really so important how can drusen volume be so important? Okay.

So we know that we can measure drusen volume using these – we can measure drusen using enface images as well and you’ll stack it all up and look at this sort of the OCT fundus images as it was
called. And just as a matter of reference as how far things have gone, you know this C mode or coronal kind of view, that is looking at the layers directly, hasn’t been around all that long. And I’m going to show you – this is a patient with drusen and one of the first C modes done I think was done of a patient, this patient. And we have this little movie, you can see how crude this movie is and Herochi Ichikawa and Larry Hageman worked on this, but you know obviously you saw some really elegant movies, but this was not that many years ago. This field moves very, very fast, and you can see where this line comes across all these drusen tops show up and so now we have a way to measure drusen volume.

Okay, so here’s a patient with lots of drusen in the left eye, and here is the enface image. Now if you are going to measure drusen area based on the projection of this enface image it might be different than looking at a color image. And this is the other eye on the same patient. But you can use some schemes to detect what you think are drusen in this enface image. You can do point to point correlations as well. And Carmen showed you, you can develop these C mode plots or essentially contour maps of the drusen on the Brook’s membrane. And you can measure their volume. And this is the same image, this came out of the BGR, I think that’s where it was published. The thing that I wonder though is whether this data is going to be relevant.

And one of the things that we looked at, myself, Peter Brennan and some of our colleagues at ARBO this year, we, we wanted to compare the drusen area as obtained by looking at this enface images versus ones coming from fundus images. And just to make a long story short, you know we, we used
fairly traditional techniques to measure the drusen area on the color images that is using our program and so let me just show you an example here.

Here is an eye that has a fundus image. This is the detection of the drusen on that algorithm that’s just used for area of drusen, and then enface you can also use a similar program to measure the total drusen area. So if you use it, if you measure it in these two ways do they agree? Well, not so well. If it agreed this line wouldn’t have a slope. So essentially what we found is on the fundus images you are going to see more drusen, there’s going to be greater drusen area than on the enface image.

In fact it might be like 20, 30, 40, 50% more. And that’s actually what was recently published by another group, Cynthia Toth at Duke. She did something very similarly and she found that – she sort of spun it a different way and said the agreement between the enface images and the color images was pretty good, about 80% of the pixels agreed. But if you look at it, for instance of the total area in her paper identified as drusen on fundus images only 80% were identified as drusen on spectral domain OCT. So there’s not a match here. And it goes right to the point of what exactly is a druse, how are we going to define that? Then another question that comes up, are changes in drusen area really relevant? If you monitor drusen area over time let alone drusen volume, do changes over time have any relevance?

And we had all these patients, as you know, and we already analyzed them for drusen area so we looked at a bunch of variables that might change over time to see whether there was a signal that might predict when these patients might convert to wet AMD.
And we used longitudinal regressive, regression analysis to find the risk profile and so forth. And one of the key things that we found was that temporal changes in drusen area, that is changes in drusen area over time and changes in the number of drusen of a particular size over time didn’t seem to be very relevant, at least in our subset which was quite a few eyes and they were followed for quite a reasonable length of time. So we didn’t find that signal. So there’s a lot of work going to be done on drusen volume, but I’m just saying back up a bit, I have questions as to whether this is going to be relevant.

And I mentioned the, the conundrum we are in as far as how do you define a druse? Probably going to have to have a group of people come together and decide whether OCT presence has to be used as well. So I’m just saying I don’t think drusen volume at least at this point we are not really sure whether it’s relevant, but it’s going to be interesting to see those folks that are looking at it.

Just a few other comments, geographic atrophy is another form of end stage AMD, that’s not the wet form but it’s the atrophic form. The reason I mention geographic atrophy is because there are some companies that are making drugs to decrease the progression of geographic atrophy. One of them is Neurotech, there are others as well. They, they use a device that’s implanted in the eye, sort of slow release to slow the regression, but that’s not FDA approved. But anyway on geographic atrophy because of the reflectivity on an OCT you really could measure it quite nicely the size of the geographic atrophy and do some serial measurements.
And this – my last slide has to do with there are folks that believe that drusen types of very important. You’ve heard of soft drusen. My problem with the definition of soft drusen, the drusen can be soft but if you make it smaller and smaller and smaller, all of a sudden the borders can’t be soft because there’s no – there’s no change in the area. I mean so I think it’s sort of a construct, but there’s also this called reticular drusen, and here’s just an image came up from Holtz who has a paper this year. Reticular drusen are ones that you see on fluorescein angiography and they, they show up as dark little spots and if you image those on OCT they look a little bit different than some of the more standard AMD drusen. So anyway you could subcategorize drusen with respect to OCT.

But I guess in closing here I’ll just say OCT has given us so much more information and now how do we use this information because we have so much data that we can look at and so the data manipulation becomes very, very important in any kind of trial. Thank you very much.