Good afternoon, my name is Kevin Gibson and I will be talking about idiopathic pulmonary fibrosis, a disease that we are studying at the University of Pittsburgh Center for Initial Lung Disease and one in which we’ve been involved with more than a decade. So the objective of my presentation really is to provide you with an overview of the classification of interstitial lung diseases, the so-called idiopathic interstitial pneumonias, we’ll describe some of the major clinical radiographic and pathological features of the idiopathic interstitial pneumonias, I’ll point out some of the pitfalls in diagnosis and management of these patients and finally will emphasize the important role of clinical trials and emerging areas of research, particularly in biomarkers.

So idiopathic pulmonary fibrosis is really a disease that has witnessed a dramatic evolving classification since the 1970s, in the 1970s we considered this really a heterogeneous population of diseases that seemed to have a highly variable clinical course and relatively resistant to medical therapies. It was really under the leadership of our pathology community and with the advent of high resolution CT scanning that we came to recognize that in fact the idiopathic interstitial pneumonias represent a variety of distinct clinical pathologic and radiographic entities which carry a unique prognoses and this was really made very clear around – in the early 2000s.

And so this classification led to the scheme that idiopathic pulmonary fibrosis represented a unique disease within this category which demonstrates pathology of usual interstitial pneumonia, but then there are other diseases as well that are described in this slide, in fact I think the next slide provides a listing of this. Nonspecific interstitial pneumonia, which is a idiopathic entity in some cases but more often is associated with either a connective tissue disease or with hypersensitive pneumonitis,
acute interstitial pneumonia, desquamative interstitial pneumonia and respiratory bronchiolitis with interstitial lung disease and finally cryptogenic organizing pneumonia makes up the final of the classifications of the idiopathic interstitial pneumonias. And the important issue I think in this classification is that of all of the diseases described idiopathic pulmonary fibrosis is one of the more common diseases and it’s one that carries the worst prognosis, and so the real challenge is distinguishing it from the other members of this classification scheme.

So why is idiopathic pulmonary fibrosis so important? Well the prevalence of the disease is much higher than was originally thought and we don’t really have a good handle on exactly how common it is. The most recent estimates describe approximately 89,000 cases in the United States with an incidence of about 34,000 new cases per year. The onset generally occurs between the ages of 50 and 70 years of age, and the clinical presentation is really quite protean, patients can present with progressive dyspnea on exertion, paroxysmal cough that’s usually nonproductive, it’s often discovered when the primary care physician hears abnormal breath sounds on auscultation, and patients will go on to have a chest x-ray that may show some reticular shadows but really the high resolution CT scan has really been the pivotal tool in establishing the diagnosis of IPF. They often will have restrictive lung physiology on pulmonary function tests but if they are caught very early pulmonary function tests can be nearly within normal limits.

And it’s an important disease because of its prognosis, and this has been recognized for more than a decade that even on immunosuppressive and corticosteroid therapy idiopathic pulmonary fibrosis carries a poor prognosis with a median survival somewhere between 2 ½ to 3 ½ years as described in
the first graph of work that was published a number of years ago by Daniil, and even when compared to all of the other idiopathic interstitial pneumonias described in the second graph, a UIP, or idiopathic pulmonary fibrosis is the disease that carries the worst prognosis even in patients who were treated back at that time with Prednisone and corticosteroids. And so this is a disease that really is an important disease to recognize primarily because of its poor prognosis.

Now the diagnosis of idiopathic pulmonary fibrosis can be made without a surgical lung biopsy and I’ve modified this slide because in fact the original criteria that were established by a joint statement by the American Thoracic Society and the European Respiratory Society did not at that time appreciate the pivotal role that HRCT scan would play in diagnosis. And so I believe I’ve captured the approach by most centers that focus on this lung disease in that the most important criteria that we use in establishing the diagnosis is obviously the recognition of lung scarring on radiographs excluding other known causes of interstitial lung diseases particularly the connective tissue diseases and hypersensitive pneumonitis, and then of visualizing classic abnormalities on HRCT scan which I’ll describe in my subsequent slides.

The original ATS criteria also included a bronchoscopy to exclude other known causes of disease, I believe in the United States this is not a common approach that’s taken primarily because of the limited utility of bronchoscopy and transbronchial biopsies in helping us in diagnosing the idiopathic interstitial pneumonias, and the other criteria, abnormal pulmonary function test I think has gone to the wayside as well primarily because HRCT scan has become such a useful tool that we can capture the diagnosis often in patients that have very, very few abnormalities in pulmonary function testing.
I think the mono criteria are also important generally speaking, most of these patients will be over the age of 50 and if they are not over the age of 50 we tend to lean more on surgical lung biopsy in establishing the diagnosis. They often have the insidious onset of unexplained exertional dyspnea usually with the duration of the illness lasting greater than 3 months, and often but not always one can hear the classic bibasilar dry Velcro type inspiratory crackles on auscultation.

The radiographic features of idiopathic pulmonary fibrosis are probably the – extremely well characterized and it’s really become the most important way of establishing the diagnosis outside of a surgical lung biopsy. So the first image I’m showing here is a image of a low resolution CT scan and one can appreciate there are some reticular shadows visible in the subpleural areas of the lung, but it’s really high resolution CT scanning that captures the abnormalities of IPF the best. And the abnormalities that one seeks in establishing the diagnosis is the presence of subpleural honeycomb change typically in a basilar distribution and these are associated with increase in interstitial markings, areas of traction bronchiectasis, of bronchiectasis that’s the result of surrounding scar tissue which essentially pulls apart the bronchiolar structures, minimal alveolar or air space disease. If you have lots of air space disease it really is – should suggest another diagnosis, although you can see this with IPF. And all of these features are best seen on high resolution CT scanning. So in order to establish a diagnosis one has to have the capacity for performing CT scans with optical sections of less than 1.5 millimeters.
Now in instances where the CT scan abnormalities are not classical, and this happens in our experience in around 40 to 50% of patients, then a surgical lung biopsy becomes an important tool in establishing the diagnosis. Now most often this is done with a video assisted thoracoscopic approach, it carries the lowest morbidity and mortality. It’s important that the surgeons who performs the procedure sample multiple lobes and also areas that are least involved by the disease so that the pathologist can actually visualize the early aspects of the disease process.

It’s also important to avoid the right middle lobe and lingular which are tempting structures for the surgeon to sample because these are area of the lung that carry the most – that most often carry nonspecific changes. And critical in surgical biopsy the diagnosis of IPF is to have an expert lung pathologist, otherwise the procedure is really of limited value. Any surgeon can sample the lobe, really the answer is going to be found on the pathologist’s bench. Fortunately there has been a proliferation of lung pathologists with lots of expertise in the disease and so surgical lung biopsy is becoming a widely used tool in establishing this diagnosis.

And to give you some examples of how the idiopathic interstitial lung – pneumonias appear on histology, the first slide here I’m showing you is a slide that shows a section through a lung that where the alveolar structures are quite thickened and fibrotic and there are numerous cells, macrophages within the air spaces. This would be the pathology of a disease that has a sort of a temporal homogenous appearance with desquamating cells – the appearance of cells that are filling the air spaces would be a typical appearance for the disease desquamative interstitial pneumonia.
This slide shows again a temporally heterogenous process that is all areas of the disease process appear to be at the same stage, only in this case the alveolar receptor again thickened but lined with numerous inflammatory cells that are dispersed evenly throughout these alveolar structures. This would be the pathological appearance of a section through nonspecific interstitial pneumonia.

The last slide has a quite unique appearance in that the lesions appear to be temporally heterogenous, in that where the disease process occurs one finds areas that are affected to a minimal degree as might be seen in the upper outer corners of the lung, in areas interspersed with areas that are affected to a large degree as evidenced by the intersections, the right sided aspects of this slide and it shows basically very, very thick regions of fibrotic tissue interspersed with areas of normal lung, some of the fibrotic areas have honeycomb change that are filled with inspissated mucous, and the arrow points to an area of the lung that shows relatively fresh collagen deposition as evidenced by its hypereosinophilic appearance. This would be a pathologic disease that a pathologist might describe as a temporally heterogeneous lesion with areas of lung remodeling, a pattern that would be very typical for the pathology of usual interstitial pneumonia and would suggest a diagnosis of IPF.

Now it’s important to recognize that the pathology of usual interstitial pneumonia and even NSIP, nonspecific interstitial pneumonia can be seen in other diseases, and so it’s pivotal in establishing the diagnosis that you exclude as best as possible some of these other diseases. So for example chronic hypersensitive pneumonitis can often have UIP pathology, the clue may be on lungs, on slides that you might see some poorly formed granuloma that might suggest a diagnosis. We see a lot of UIP in association with dermatomyositis, particularly the antisynthetase syndromes and some of these
syndromes or rare antisynthetase are harder to diagnose because many of the tests are not commercially available and so it’s important to give this disease consideration in patients, particularly if they are under the age of 50. Scleroderma, rheumatoid arthritis and mixed connective tissue disease can also have an association with their disease systemic manifestations, the pathology of usual interstitial pneumonia as can microscopic polyangiitis. And the real question that we have nowadays is when you see UIP in association with these other diseases it doesn’t carry the same prognosis. Our general sense is that it probably does not, particularly if you are able to control the underlying secondary disease, for example removing patients from their exposures in the case of chronic hypersensitive pneumonitis or providing immunosuppression in patients that have active systemic autoimmunne inflammation that they may carry a slightly better prognosis.

Now IPF is an interesting disease in that it has a highly variable clinical course. The disease is thought to have a phase where you can see a very gradual decline generally associated with the appearance of these advancing lesions we call fibroblastic foci and that this decline can be punctuated by more rapid periods of progression which we call acute exacerbations and these acute exacerbations at times can be quite dramatic and lead to the rapid progression of the lung disease and often death within 3 to 6 months after their onset. And so it’s a disease that’s highly variable and highly unpredictable where you can have prolonged periods of relative stability sometimes lasting months to years punctuated by these periods of fairly rapid lung disease progression.

And in fact this was really best captured in data that was published a number of years ago by Dr. Martinez where he looked at the survival of patients in the placebo control arm of a large clinical
trial of – that was conducted by interview and of a drug called Interferon Gamma, it was one of the first clinical trials in IPF. And he looked at the physiological patterns that proceeded IPF related death in the placebo control arm. And each slide here is depicting a person, it’s a favorite – we call this our spaghetti graph. What it shows is that if you look at for example A-a gradient prior to death that the numbers are all over the place, physiological parameters such as percent FVC did not seem to follow a decline prior to death, nor did even the fusion opacity often times remain relatively stable prior to patient demise. And so what this slide really tells us is that physiological parameters that we typically follow in monitoring disease process are really quite poor predictors of advancing disease or poor predictors of long – of short term prognosis.

And this has been one of the principle reasons why we have embarked on an effort that began more than a decade ago in searching for peripheral markers, biomarkers in the blood that might help us in defining or at least predicting the clinical outcome of patients that have idiopathic pulmonary fibrosis. And in fact the NIH has been very strongly behind this notion of a biomarker to come up with a definition that’s been very useful in understanding the role that these biomarkers may play, they define it as a characteristic that is objectively measured and evaluated as an indicator of a normal biologic process, a pathogenic process or pharmacological responses to a therapeutic intervention, it’s a relatively broad definition but I think it captures two important aspects of biomarkers that have been important, that we think would be important in the future in understanding and predicting the clinical course of this disease.
And one aspect is that the biomarker may reflect key events in disease pathogenesis and so it may be important in evaluating a particular drug therapy or it can be an epiphenomena. It can be sort of an instant bystander, the so-called canary in the gold mine, it changes, has relevance to a disease process without necessarily being an important parameter of disease pathogenesis. And so we’ve looked at a variety of biomarkers and have validated these in separate cohorts of biomarkers for example in MMP7 which is depicted in the first graph seems to be a very, very useful biomarker in predicting or segregating patients that are more likely to have a progressive disease with a high mortality rate as shown here in the red solid line those that had very high levels of MMP had a median survival around 2 years compared to those that had very low levels of MMP7, their median survival was somewhere around 4 ½ years. The same was seen with MMP7 when we looked at progression free survival that those that had very high levels of MMP had a progression mean survival that was less than a year whereas those that had low levels had a progression free survival of more than twice that number. And we found very similar results with VCAM1, S100A12 and IL8 all of these have been validated in independent cohorts and it basically validates the notion that a peripheral biomarker may be a useful parameter for segregating patients that have a poor prognosis at the time of diagnosis with IPF.

We’ve also in collaboration with Dr. Duncan have looked at circulating T lymphocytes in a peripheral blood and they seem to carry information that has enormous prognostic value as well. So through Dr. Duncan and his lab demonstrated that C28 downregulation on circulation CD4 positive T cells was associated with a very poor prognosis in patients with IPF as depicted in this slide where the median survival of the downregulation could be as much as – as low as 2 ½ months whereas the
median survival in patients that had high levels of circulating CD28 positive T cells had a much better prognosis.

We’ve also looked at gene expression profiling in patients that have IPF and in this study we looked at peripheral blood mononuclear cells in expression profiling and identified a number of genes associated with T cells including CD28, ITK and ICOS, all of which when down regulated were associated with a poor prognosis in the University of Pittsburgh IPF cohort demonstrated on the left hand side and this was independently validated in a separate cohort at the University of Chicago where very similar findings using a completely different platform, a completely different population that was not transplanted yet these genes turned out to be very important in predicting survival. And so it’s very clear that there are peripheral signatures in the blood that provide a great deal of information on prognosis and clearly this is going to be a focus I think of research in the future in attempts in identifying biomarkers that will allow us to predict how this disease will behave.

Now with regard to therapy there have been a lot of historical approaches to therapy that were based on the notion that IPF must be an inflammatory disease that eventually leads to lung scarring. And this concept was probably first evident in the 1950s when we were using lots of corticosteroids to see if we could affect the prognosis, and unfortunately in the majority of patients even at that time when the classification scheme was not quite as complex as it is today many of those patients failed to respond to corticosteroids and so immunosuppressive drugs were tried such as Azathioprine and Cyclophosphamide and I’ll show you some of that data in just a moment. It proved to be not particularly effective as a therapy for IPF as well. Antioxidants such as a Glutathione and N-
acetylcysteine, the latter of which is still arguably used today, had been tried and I’ll show you some of that data. In my opinion it probably doesn’t offer much in the way of hope for patients with this disease.

The next, the focus I think in the future has been really trying to develop drugs that attack fibrosis, the so-called antifibrotic drugs. The earliest that have been tried have been Colchicine which we believe probably offers little benefit, D-penicillamine which has been studied and found to be of limited value as has been Interferon Gama in a large clinical trial and Interferon Beta both of which failed to meet their primary end points and have been found to be of limited value as a treatment.

More recently immunomodulators have been explored. Etanercept was investigated in a large clinical trial and found to be not of particular value for patients with IPF, Pirfenidone is a subject now of a new phase III clinical trial, it’s been studied in 2 phase III trials in the past, one of which met its end point and the other which did not. So it was not approved in the United States, but it is being studied again in another phase III trial and it’s hoped that this will probably be one of the first drugs available in the United States. It is already approved in Japan and in Europe as a therapy for IPF.

So unfortunately in my experience despite the evidence corticosteroids are still used quite often in patients with IPF. And there probably is a rationale for it in terms of symptom management, it does seem to help some patients with cough. There has been some rationale offered that it may slow the inflammatory phase of this disease although there is little evidence to suggest that’s true. Some
people argue that when patients are removed from corticosteroids the disease seems to progress and so these are all – providers compelling arguments for using steroids, but unfortunately corticosteroids are drugs that have terrible side effects in the population of patients with IPF particularly because of their advanced age and their comorbidities and so we are strongly against the notion of using peripheral corticosteroid therapy even in patients with protracted cough. We tend to go with inhaled corticosteroids to minimize some of these terrible side effects.

Now Azathioprine and Prednisone is still used often in Europe, the evidence provided for their use in a study that was done not too long ago in 1991 by Dr. Ragu where he compared Azathioprine Prednisone compared to Prednisone alone in patients with IPF. It was a very small study and the yellow line suggests at least that patients who were on Azathioprine and Prednisone had a slightly better prognosis, unfortunately the study was somewhat marred in that at least one individual in the Azathioprine Prednisone group switched to the Prednisone group alone because of intolerance of Azathioprine and two people in the Prednisone group had Azathioprine added and one person in the Prednisone group actually committed suicide, and so with such small numbers the data is really quite lacking in terms of significance.

We’ve looked at a combined corticosteroid and Cyclophosphamide in a study that was done by Dr. Collard a number of years ago where he didn’t have a true placebo arm but he looked at the expected survival and those – I’m sorry, there was a placebo on those that were untreated had a median survival that was essentially identical to those that were receiving combined corticosteroids and Cyclophosphamide, and so it doesn’t appear to offer any real benefit in patients with IPF.
A trial that has gained a lot of attention more recently published in a very high profile journal, The New England Journal of Medicine in 2005, was the IFIGENIA trial. This was a trial that looked at N-acetylcysteine as a therapy for IPF. The trial was somewhat flawed in that there was no true placebo arm, the active treatment group received N-acetylcysteine combined with Prednisone and Azathioprine and the control group received Prednisone plus Azathioprine alone. There was 182 patients randomized, 155 were included in the analysis and the treatment was a one year therapy. And what they showed is that at least in their data set that the N-acetylcysteine treatment group, that is N-acetylcysteine plus Prednisone plus Azathioprine seemed to have a slower decline in vital capacity during the 12 months of observation compared to the placebo arm, which included patients on just Azathioprine and Prednisone alone. And they saw similar data, a more gradual decline in defusing capacity comparing the two groups. There was no difference in survival at the end of one year.

The study has been heavily criticized because of the very high dropout rate seen in both the treatment and the placebo arms, and the suspicion, or at least the concern that there is not a true placebo group that was compared, and it’s possible perhaps that N-acetylcysteine, the benefit it offered may have been in abrogating perhaps some of the side effects associated with Azathioprine and Prednisone and not truly a therapeutic effect. Nonetheless this study has led to the wide use unfortunately of N-acetylcysteine alone as a therapy for patients with IPF. Fortunately it’s not a particularly toxic drug, but there is little evidence that N-acetylcysteine alone offers any therapy for IPF and in fact this is a topic that’s currently being investigated in a large trial sponsored by the NIH,
the so-called PANTHA trial which hopefully we’ll be seeing some results from that soon. That trial does include a true placebo arm.

So the first step we take at our center is really the integrated approach that focuses on preserving quality of life in patients with IPF. And we found that the best way to accomplish this is ensuring adequate oxygenation at rest, during sleep and with exertion. The oxygen equipment available today can provide a great deal of freedom for patients, particularly in travel the new portable concentrators have been particularly useful in this regard. We believe that pulmonary rehabilitation is an important part of management of these patients that you can see dramatic improvements in 6 minute walk distance and exercise capacity in patients that participate in pulmonary rehab, particularly with adequate oxygenation. We encourage our patients to enroll in clinical trials of mono therapeutics because we believe this is the only – this offers the only hope for bringing forth a drug that may offer a benefit to patients. And I’ve found that my own personal experience, providing an opportunity to participate in a clinical trial often gives patients a great deal of hope and confidence, so they can get on with their lives in the hope that they might be exposed to a drug that may prove down the road to be of benefit in prolonging survival.

And then finally in patients that are appropriate we recommend early referral for lung transplantation because lung transplantation really offers the only hope for long term survival in the majority of patients with this disease. The numbers are not perfect, you know I quote a one year survival of around 90%, a 3 year survival of around 70%, and a 5 year survival of around 50%, emphasizing the importance and recognizing that they are trading one disease for another disease. Although one of
my patients who were transplanted reminded me that they often are trading – they are also trading the possibility of life versus death, and those that get transplants that do well that certainly is the case for most of those patients.

And so you know for clinical trials there are fortunately a lot of trials that are available in the United States. These trials are published online in clinicaltrials.gov. There probably have been more than 10 trials that have been completed that failed to demonstrate a benefit of the drugs in IPF, but there are newer drugs that are being studied that look very, very promising and so I think it’s important to provide patients with an opportunity if possible for participation in one of these trials, it’s the only hope that we have of providing a drug that may offer long term benefit for these patients.

And so in summary idiopathic pulmonary fibrosis is a disease that we are seeing very commonly now, I believe it probably will come off of the NIH Rare Disease List soon because the diagnosis is being established very frequently with increased awareness on the part of primary care physicians and the wider use of HRCT scans. And it’s important to recognize that this is a disease that carries a poor prognosis and that the best hope for patients really is enrollment in clinical trials and if possible a referral for lung transplantation because it’s clearly the hope is that we can provide these patients with not only a longer life but a higher quality of life as well. And with that I will conclude my remarks. Thank you.