Realizing that there is incredible heterogeneity in this audience from individuals who are card
carrying pulmonologists to folks that are molecular biologists and internists and so I'm going to do a
little bit of an introduction for COPD which I'm sure will be redundant for some of us.

COPD, the most recent GOLD Guidelines and if you want a nice executive summary of COPD with
regards to state of the art pathogenesis and treatment options goldcopd.org is a website that has free
downloads, good stuff. So COPD as defined by this group is common, preventable, treatable,
partially reversible. In part that's marketing from when we used to say it's a disease, they did it to
themselves, let's move on, okay. It's characterized by persistent air flow limitation and it's usually
progressive and disabling even after individuals quit smoking. It's associated with a chronic
inflammatory response and while this is second nature to us now 10 years ago, 15 years ago this was
a novel concept in the airways and the alveoli to noxious particles or gases and both chronic
bronchitis or emphysema the classic definitions fall under the category. More recently exacerbations
and comorbidities contribute to the overall severity.

I was looking if I played with that from what I've learned in the conference if we were to define
aging it might have some of these components. It's definitely common, preventable, treatable and
partially reversible I think needs to be proven. It would be nice. Definitely progressive, disabling,
associated with a chronic inflammatory response as I've learned and comorbidities no doubt
contribute to the overall severity so there clearly are overlaps in the definitions.
So COPD is no longer the fourth leading cause of death in this country, it was supposed to become the third leading cause in 2020 and some people still have those slides, it's the third leading cause. It passed up stroke a couple of years ago. As of 2012 over 140,000 people in the United States died of COPD and by the way women are dying at a greater frequency than men as of early last decade, another stereotype broken. It is a disease that unquestionably increases with age, and this is showing the incidence in decades of life, fairly infrequent in your 30s, some in your 40s, but really almost exponentially rising in later life. It's estimated 1 out 4 individuals throughout their life will achieve a diagnosis of COPD.

This concept was brought up earlier yesterday, it's the fact that procreation and evolution really didn't ever discuss COPD because people didn't live long enough to have COPD. And in the 1900s the average life expectancy was 48 years old, 1940 it was 58 and 2011 it's in the mid 70s. These are the normal deterioration with aging over time and FEV1 about 25 ml per year. Today very few people reach an age to become respiratorily disabled and definitely not dead due to respiratory issues because of their age. Although we live to 120 or 130 then maybe it will reach that curve. These other 2 lines, 40 ml per year is about a moderate decline in COPD and 75 ml per year would be a somewhat more aggressive decline. Back at 1900 even the more aggressive COPD would not have killed the average person and more moderate COPD as of the 1940s would really not even have caused disability. And so it's really a manifestation of us living long enough to achieve enough deterioration to have disability and ultimately death. And that's why this disease has become much more popular lately.
COPD: AN EARLY AGING DISEASE?
FRANK SCIURBA, MD

COPD as far as classification if you had to pick one number to classify it, and as you'll see my belief is it's incredibly complicated, but if I had to pick one number I would still pick this number. I hate to have to only pick one number and that's FEV1, the amount of air you could forcibly blow out in one second. And we define obstruction by that amount of air divided by the total air you can exhale, the FEV1 to FVC ratio. And GOLD which is now the most common definition, it's like blood pressure 120/70 is normal, GOLD says just to make it simple that if your FEV1/FVC is less than .7 you have obstruction. These other categories are just general categories of rating severity, but that point of a ratio of .7 being relevant is relevant to this next slide.

So the other way to define an abnormality is to standard deviations from the mean, which is the way we define most laboratory tests as abnormal. And if you chose the lower limit of normal which is the way the American Thoracic Society/European Respiratory Societies define it by using that value of .7 which is now increasingly common the definition of obstruction interestingly you wind up severely overdiagnosing COPD the older you get. In fact the lower limit of normal for a 90 year old is a ratio of .62, which is well into obstruction. So I think it's fair to say that using .7 in really old people doesn't tell you who is abnormal relative to the population. On the other hand, severe coronary artery disease may be normal in a 90 year old too, and so I'm not sure that it's not clinically relevant even though it's really been a point of discussion with regards to what we should use as defining normal. So that's an issue relevant to age and how we define the disease as individuals get older.
Now the first time I heard about lung age being relevant was almost 3 decades ago when Tom Petty who most of know as the - not the car driver or the singer but probably the most influential person in clinical pulmonary disease in history and came to our hospital as a visiting professor and he said the way to get people to quit smoking is to shock then and tell them how old their lungs are. And to this day I do that in clinic and it is I believe the most effective way. I look at their PVTs, you have the lungs of a 90 year old. It scares them, it really does. I think what it says is that people respect being old age more than they do their COPD and they don't want to go there, but they don't really care too much about the COPD. So you've got to change their disease, which is why this conference may be a really good thing. We can change COPD to getting old people, may want to treat it.

So this actually was reflecting a couple of publications at that time, Morris said that you know I use it that way, but it really wasn't proven until 2008 when a little randomized study of 560 individuals they gave them their randomized to giving them their lung age from the PFTs or just doing PFTs and giving them a random number. And they doubled, all patients went through a intense smoking cessation program, they doubled the quit rate by telling people their age as I just did. And so and basically the way that works is if this is the normal curve, the range of normal and you have - you are a smoker and are susceptible and you have COPD then basically say if that's your PFTs then you have the lungs of a 75 year old even though you are 50. And that's sort of how you do it to your patient as well. So it works.

So what's interesting is if you look at the physiology of aging in fact it very much reflects the abnormalities that you see with COPD. The FEV1 normally drops 20 to 30 cc per year, and as we
just showed and of course that happens in COPD. The residual volume which is the air that's left in your lungs at the end of a full expiration winds up increasing over time and that number actually has been shown to be more relevant to symptoms than the FEV1 is, it's just harder to measure and so we don't use it as regularly. But that amount of air left trapped in your lungs goes up over time. It's probably related to loss of lung recoil, early closing volume of the airways, the air stops coming out, also changes in chest wall compliance, you can't exhale as completely. Probably multiple factors, probably different factors in different individuals which is my usual theme, but that happens. Diffusing capacity drops, probably related to what we'll discuss early progressive anatomic loss of alveoli in these patients.

AAO2 gradient, transfer of oxygen, arterial oxygen saturations drop as reflected by the AA gradient at about 1 mm of mercury every 5 years. Dead space increases from age 18 to 89, normal aging your anatomic dead space increases by 100 cc, oxygen consumption which declines a measure of maximal exercise with aging just as it does with COPD. And while with normal aging we don't get hypercapnic, your hypercapnic drive to a challenge decreases as it does with COPD. So in fact there are a lot of things physiologically that are in common.

COPD is actually a heterogenous process, it is caused by cigarette smoke but it can cause airway fibrosis and remodeling and it can cause emphysema or parenchymal destruction, two very distinct histologic processes that in fact likely reflect very different biological processes which has been our theme. And it's plausible, and I would put the hypothesis forward here that not all COPD is senescence or age related but that there may be some sub-phenotypes and by classifying and
recognizing these sub-phenotypes it potentiates our ability in fact to make the discoveries, which is why I actually became relevant at an NIH level because the molecular scientists wanted well characterized and classified patients to bring out their molecules.

So these are the two extremes. The person on the left is somebody who has COPD related to alveolar obliteration, the density of that lung, the dark lung, very little lung tissue; the person on the right has relatively normal parenchyma. They both have the same FEV1, the gold standard that we define the disease but the person on the right has relatively little emphysema to the one on the left. When you look at this that clearly suggests very different processes. In fact we believe COPD is likely many different diseases mitigated by hey gene environment interactions. How about that? And I think that that's very likely the case. We define it as a syndrome very naively but they are likely very different biological processes.

The other aspect of COPD is that it is associated with comorbidities. And your first reflex is to say well they smoked, smoking causes all kinds of bad things. But the odds ratio for any one of these comorbidities on this list if you have COPD and you are a smoker goes up if you have COPD. And we'll talk a little bit in more detail about depression, osteoporosis, vascular disease, lung cancer, all linked with the biological processes of COPD and the classic systems biology way that we don't yet fully understand yet.

This is a recent publication showing all of the comorbidities in a basically a historical and DRG related analysis that are greater than 5% of the COPD population. And sure hypertension is common
but it's more common if you have COPD. Arthritic issues, obesity, metabolic syndrome is more common if you have COPD even though cachexia is also common, two very different phenotypes. Heart disease, vascular disease, diabetes, kidney disease, all of these things, more common if you have COPD. Cachexia, muscle wasting, one of the original things recognized to be linked we often used to in an almost derogatory way refer them to pink puffers, there was this skinny guy struggling to breath. We thought it was just increased metabolism but there may be in fact these inflammatory mediators or senescent issues, senescence issues that may be causing these.

This is a group of 57,000 plus COPD discharges in a regional health initiative and they looked at those patients that had also coronary artery disease or congestive heart failure and almost half of all the patients with a diagnosis of COPD discharged from the hospital had a cardiac issue. I would challenge you that not half of all discharges from the hospital have cardiac issues, so it enhances it.

This is an analysis from our SCCOR cohort. We looked at variables within our large database that predict depression and depression is associated with a decline in lung function, FEV1. Female gender, ongoing smoking status but interestingly the senescence maintaining cytokine IL-6 is also independently associated with depression in the setting of COPD.

The Scottish group looked at pulse wave velocity, a measure of vascular function, and found that it is associated with obstruction, FEV1, with a modest R value correlation coefficient. But if you now sub-phenotype it into severity of emphysema holes in the lung and not the airways it's actually tighter, so vascular dysfunction, the systemic process seems to be more associated with emphysema.
Jessica Bon in our group is making her career in looking at osteoporosis and its relationship to emphysema, and just looking at the slides, normal lung, normal bone might be intuitive, maybe there is something going on there that might be linked with destruction of matrix, and in fact Jessica showed that there is no association with FEV1 but there is an association with holes in the lung cause holes in the bone and so osteoporosis linked with emphysema. Of course it's also associated with steroids but that was the emphysema was independent of any other factor.

David Wilson in our group showed that if you have emphysema and just look at these GOLD 3, 4, the most severe patients as far as obstruction if they don't have emphysema 0 out of 63 in the top, 0 out of 63 have cancer, whereas if they have emphysema and severe obstruction 10% of those patients in the cohort developed cancer. So emphysema independent obstruction predicts cancer.

So we showed that physiologic changes are in common between COPD and aging. We showed - we discussed that in fact with senescence you get loss of alveoli, you get the equivalent of emphysema, decreased lung attenuation. And there has been a lot of discussion in this conference of immunologic changes associated with aging, and many of them overlap. There are some differences between COPD and senescence but in fact there are many things that overlap including IL-6 and IL-8 which are very commonly found to be elevated both locally in the lung and systemically in COPD.

Steven Duncan and Jessica Bon and Divay Chandra have been working with autoimmunity in COPD and in fact we find that 96% of our patients have autoantibodies, and they are in a nonspecific
pattern but they are in a pattern that you might see with enhanced autoimmunity associated with aging or other chronic diseases. And in fact these autoantibodies do abnormally attach to epithelial or endothelial cells, different in different individuals.

This is a wonderful review and all the numbers there I think are meaningful in showing that all these are really validated with the literature. Kumar showed that there is a very similar pattern between that senescence associated secretory phenotype that had been discussed earlier and what we see with COPD. And so the inflammatory response, the proteases, growth factors, etc. seem to be very similar between the processes. In fact there has been now a number of provocative editorials in our literature in really discussing this concept of senescence in COPD and that in fact environmental toxins, etc. can in fact through all the mechanisms discussed in this conference create really a senescence state releasing the mediators that in fact maintain that vicious cycle. All of the things in this diagram that's been shown several times out in Lopez I can find literature support for everyone of these hallmark events of senescence that occur in COPD, telomere attrition, epigenetic alterations, unfolded protein response and I think it's valid.

So in conclusion I think the use of an absolute I think the use of an absolute ratio overestimates the prevalence. Many physiologic anatomic cellular perturbations are common between COPD and aging, the vicious cycle of inflammation and repair in fact may lead to premature cell senescence and early aging mechanisms facilitating the pathology in COPD and I believe attention to the categorization of phenotype variation within the COPD pattern and its comorbidities may facilitate the understanding of the impact of these aging mechanisms in the pathogenesis.
And I'll end with this slide, this is my father who passed away in April with his great, great grand-nephew who is more than 100 years younger than him playing with his Oxymizer. My dad had over 100 pack year tobacco history, quit in his 50s, smoked a lot in World War II and afterwards. He was on oxygen for a few years and I figured there was not much I can do, he had a PCP in Chicago that wasn't very aggressive and toward the end we saw a CT scan and he had both horrible emphysema and progressive IPF, both disease processes very active. And I because of all of you I think have much greater insight into why this happens, and in fact it's probably normal for a 100 year old 100 pack year smoker.

So a lot of collaborators, I'm a team scientist. I've had a PO1 but never an RO1 and it's because I work with people and enjoy it. So thanks for your attention.