Good morning. So I thought that it would be helpful to sort of go back and see what population screening for genetic disease, sort of what the definition is. And it's testing to identify people with certain genotypes known to be associated with genetic disease or a predisposition to genetic disease and that disorder may affect that individual or their offspring and the purpose is to examine individuals all individuals of a designated population regardless of their family history. And this has public health implications. And so just a little bit of history we've been doing population based screening for genetic diseases for quite some time. The first was PKU which is an autosomal condition remember that means that you need a mutation inherited from both your mom and your dad to have that condition. That testing has been happening in newborn since 1963 and carrier screening for Tay-Sachs disease which is also an autosomal recessive condition that's common in the Ashkenazi Jewish population, started in 1971 and it has led to about a 90% reduction in babies with Tay-Sachs when parents know that they're carriers. And so just to remind you Ashkenazi Jewish individuals are usually of Eastern European Jewish descent and about 95% of the United States population of Jews is of Ashkenazi descent.

So there's a long standing history of genetic testing population based in the Jewish community and it started in 2004 with a recommendation for 4 specific diseases then in 2008 to 10 and now more recently in 2014 the Victor Center which is a Jewish organization is suggesting testing for 19 different Jewish genetic diseases.
And so what are Jewish genetic diseases? These are usually, always recessive conditions when we're talking thus far, that have a higher incidence in the Ashkenazi Jews and that are caused by a founder effect. And so what is a founder effect? It means that there was a mutation or several mutations in the original founding population and that due to marked population decrease, migration or isolation either geographic or social that those mutations became more prevalent in that population and so there's a higher rate of those mutations. And so that's why genetic testing in the Jewish community has been a commonplace thing and a very well established mechanism.

There's then initiation of Pan-Ethnic screening so screening in all populations since 2001 for cystic fibrosis also an autosomal recessive condition and Pan-Ethnic screening is becoming more popular. Because as you know genetic technology is really changing a lot and our ability to look at multiple genes or multiple mutations simultaneously is readily available and becoming less and less expensive. So now there are panels that are looking at specific mutations in over 90 conditions for multiple ethnic groups. And these are usually autosomal recessive conditions and these are things that are being done sort of preconceptually so before having children. Because if both parents are carriers then they have a 25% chance to have a child with that condition. So what I'd like to point out about all of the screening that we are talking about so far is that it's screening that's looking at specific mutations. So we've identified that there are particular mutations that account for the bulk of the disease within populations. And so rather than needing to evaluate the whole gene, we can look specifically at certain areas of the gene which is more targeted.
So now let's talk about breast cancer. So you've seen this slide from me before if you look at all breast cancer currently we're thinking that maybe 5-10% of breast cancer is hereditary, meaning that it's due a mutation in one single gene. And when we pull that 5% out of that pie and look at what the causes are, we think that right now maybe the bulk of those are being caused by mutations in BRCA 1 and 2. And through this ramping up for genetic technology we found that maybe 25% of the other part of that hereditary piece of the pie are being caused by other genes that are either less common or are lower penetrants, so don’t' have the same degree of risk when there's a mutation.

And so remember that these BRCA genes are inherited in an autosomal dominant manner, meaning both men and women carry these genes and can pass them on and we need only inherit one copy of a gene with a mutation to have that predisposition to cancer.

And so right now genetic testing is currently based on personal or family history of cancer and so that's how we identify who gets tested. And the NCCN regularly changes who gets tested and each time the guidelines come out they tend to become more and more broad encompassing more people. So these are the more recent guidelines and I'm putting this up to sort of show you that there's lots of different ways someone can potentially meet criteria to be screened for BRCA whether through personal or family history but at the present time in the absence of a personal or family history of breast or ovary cancer, most insurance companies are not going to cover genetic testing. And so this idea of population based screening right now would not be covered under most insurance policies.
And so what are some of the limitations to our current approach to testing? Well if we are limiting it to family and personal history, personal history is pretty obvious, but family history we all know families work in different ways. So in some families maybe there's a lack of health history communication or in the past it was more concerning to talk about things like cancer and so it just wasn't shared information. I generalize lack of awareness, small families, maybe we just don't see things because there are too few people, inaccurate information was passed oh they died of bone cancer or lung cancer when it was really a metastatic situation from somewhere else, oh that's your father's side it doesn't really matter if it's breast cancer or ovary cancer. The family is mostly male and so if we're talking about mutations that predispose predominantly to breast and ovary cancer we'd have an inability to see manifestation of those diseases and then maybe just chance. A few women in that particular family inheriting the mutation or the family migrated and they don't really know about their ancestors. So there's lots of reasons why sometimes family history will fall short of being able to help us with identifying people who might have a BRCA mutation.

So when do we think about population based screening? Well the World Health Organization has 3 criteria and one is that the disease is an important public health burden in the identified population, that the risks of the disease and the screened population are known and that effective interventions are available to reduce morbidity and mortality in mutation positive individuals. And so up until very recently number 2 has felt to not have been known and that’s because when we think about testing and we think about all of the risks that we quote people who have BRCA mutations, that’s been all generated from families that have been selected based on personal or family history and so the concern is that maybe those data are skewed towards a higher end and that if we offered up
testing to this generalized population that we’d find that the risks for breast and ovary cancer related to BRCA 1 and 2 are actually less. And so the U.S. Preventative Services Task Force has said that population based screening is not really ready because we don’t have that piece of data. So why all the talk now about the potential for population based screening? Well I think that it’s been sort of a coming together of worlds, we all know Angelina Jolie underwent testing based on her family history and that she carries a BRCA mutation and she’s been very public about that and about her choices and so that’s really sort of generated this more global conversation about BRCA testing and the availability of BRCA testing. That sort of has come together with some papers that have been published over the last 6 or so months about population based screening and very much being pushed by Mary Claire King who as you may know was the individual who first identified the BRCA 1 gene. And so this editorial viewpoint in JAMA of September 2014 was by Mary Claire King and some of her colleagues and she’s basically saying based on our experience with BRCA testing it’s time to offer genetic testing to all women. And the viewpoint says she thinks that we need to test all women 20 and over for BRCA 1 or 2 regardless of their family history.

And she’s making that statement based on a study that she and her colleagues did in the Israeli Jewish population that also was published in September of last year and it was a population based screening for BRCA 1 and 2 carriers. So what they did as we talked about in the Ashkenazi population there are founder mutations that’s also true for BRCA 1 and 2. And so there are 3 specific mutations, two in BRCA 1 and one in BRCA 2 that are higher prevalence in the Ashkenazi population and are present in about 2.5% of the population. And this paper is stating that mutations
in BRCA 1 and 2 accounts for about 11% of the breast cancer in the Israeli Jewish population, Ashkenazi population, and about 40% of the ovary cancer.

So what this group did is they set out to recruit healthy men from various health clinics and consent them and provide counseling to them for testing for the 3 founder mutations. And when they did that, they found that there were about 175 men who were carriers of these mutations and they matched those men with men who they found in the non carrier population and then they offered up genetic counseling and confirmatory testing and those individuals who were mutation positive were then requested to offer or recruit their family members for testing. And so when they were looking at this population they were concerned that maybe these men who agreed to be part of this study were preferentially selecting themselves because they had a family history of cancer or you know had always wanted to be tested but there was no opportunity and so what they did is they looked at multiple lines of evidence to prove that this group was representative of the population. And so the evidence that they used were that when they looked at mutation frequency in the population it was similar to the studies that had been previously reported, about 2.5%. When they looked at the parental origin of the mutation it was about 50/50 which stands true, about half of the time somebody is going to inherit that mutation from their mom and the other half of the time it would be inherited from their dad.

Then what they did is they also looked at the cohort, so the age range from these subjects and when their moms would have been born, so the age range of their moms and they looked in this population they found that 9% of the subjects reported that they had a mother with breast cancer and when they
went back to the Israeli Cancer Registry for their age matched category for their moms, they found that it was about a 9% population rate of breast cancer. So they felt that based on these 3 lines of evidence that they really had a representative population that wasn’t biased. So then what they did is they tested the family members and they determined what were the cancer risks in these families that were identified via population based screening.

And so the graph on the left hand side is showing you breast or ovary cancer risk in BRCA 1 or 2 over time. What they found was that the risk for breast or ovary cancer in these women were somewhere between 70% and 80% over a lifetime which are the higher ends of risk that we have reported in the literature regularly. They also noted that there was a cohort effect and this is something that has been noted in the past that women who were born before 1958 have an overall little bit lower risk to develop cancer and that risk sort of is spread out over a longer period of their life as evidenced by the black line on the graph on the right. And that women who were born after 1958 have a higher cancer risk that sort of is shifted to a little bit of a younger age. And so in the past there’s been multiple reasons why that might be happening, some of them are just things like that are changing. Women are getting their periods at younger ages, they’re postponing childbearing, they’re having fewer children and so all of these things may be in some way contributing along with other factors that we’re not smart enough to know about and those I would say would be environmental. And so based on this information she feels that we’ve now met the who criteria number 2 which is the risk of disease in the screened population is known.
So let’s go through and sort of break down each of those criteria. The disease is an important public health burden in the identified population. Well in the United States over 200,000 women are going to be diagnosed with breast cancer this year and 21,000 women are going to be diagnosed with ovary cancer and I’d say that that’s a reasonable public health burden. So then let’s look at and if we think maybe 10% of all people, of all cancers, breast, are due to hereditary predisposition and that’s a reasonable number of these women if we just took 10% off the top that potentially have mutations and that we might be able to intervene if we knew in advance that they had that mutation.

So I’ve already alluded to the fact that mutations in BRCA 1 and 2 in the Ashkenazi population are more common, 1 in 40 or 2.5%. And when we look at the risk for a mutation in the non Ashkenazi population we see that it ranges depending on what you read between 1 in 300 people and 1 in 800 people, which is significantly smaller. The risks of the disease in the screened population are known. One we just reported on that population based screening in the Ashkenazi study that Dr. King published. If we look at another analysis of risk sort of from multiple studies, most of those studies I will say though were identified through population based or not population based referrals, but clinic based referrals or family and personal history and so they’re probably biased towards that information. But if we just look and see about risk this is average risk, so the risk for a BRCA 1 carrier who is 20 years old who has not had cancer in her lifetime age 70, maybe 50%, that’s the average risk. So we have to recognize that in some families that risk might be higher. So are these risks really different in this population based study and then this study that we got from multiple clinics. I don’t know that we can say that. I think that we’ll need to wait for some more information but through the years there have been many studies done looking at the Ashkenazi population and
the non Ashkenazi population and we really haven’t found that the risks are significantly different cancer wise.

Effective interventions are available to reduce morbidity and mortality in the mutation positive people so we’re all fairly familiar with this list; earlier screening, addition of higher more intensive screening, medicines to reduce risk and then surgery to reduce risk. So I think that we have a fair amount of data to support that we do meet this criteria number 3.

So then what are some other things that we need to think about? Well in thinking about this talk, I’m thinking about labs and what kind of testing we would need to do. So in the Ashkenazi population we only need to do 3 site testing that means it’s very specific and focused and easier really. And in the non Ashkenazi population we need to do complete sequencing of both BRCA 1 and 2 including deletion duplication studies and that’s not easy. It takes longer and it’s more expensive. Also there’s a little bit of a difference in the outcomes from testing. When you do 3 site testing the probability that we get, a variance of uncertain significance or a result that we can’t completely interpret because it’s subtle and we don’t have enough data to say is it harming gene function or is it just benign variation, it happens less than 1 in 500 times, so not very often. Where as in the Caucasian population when we do BRCA testing we get a variance of uncertain significance about 3% of the time. In other groups those numbers are higher and it’s partly higher because we haven’t tested as many people and we haven’t figured out what all the benign variation is. And so that type of a result can cause some anxiety. And then are the labs ready for the sheer numbers of people that potentially would be tested.
Other considerations; healthcare, provider education because this is not going to be the genetic
 counselors, the breast surgeons, the oncologists that are offering up this test, this is going to be
 population based screening. This is going to be your GP, your OB/GYN, so are they ready. So there
 have been a number of studies just looking at genetics knowledge in practitioners so I pulled out a
couple of those studies. Attitudes and knowledge of medical practitioners to hereditary cancer
 clinics and genetic testing, the outcome from that study was sub-optimal knowledge of cancer and
genetic testing among doctors. Specialists were more knowledgeable than GPs. Physician risk
 assessment knowledge regarding BRCA testing basically training and frequency of genetics referrals
 increased knowledge, so the more you do it, the more you know which makes sense. And then this
 last one clinicians attitudes towards general screening of the Ashkenazi population for prevalent
 BRCA and LRRK 2 mutations, that’s a Parkinson’s related mutation. This study showed that the
 physicians were more inclined to be willing to offer testing for BRCA because there were
 interventions that were more readily available and also they found that the attitude towards screening
 as correlated with the physician’s personal interests in whether or not they would want to be tested.

So if we move forward with population based testing I think we will need to make sure to have tools
available for those providers so that they can provide the appropriate patient education and informed
consent for testing. We need to make sure that we have appropriate psychosocial supports for
mutation positive people. You know we do have online supports and we have physical presence of
supports through behavioral medicine, but we need to make sure that we have enough of those kinds
of things. And do we have enough care providers to manage the risks related to the mutation
positive results. And I know that here at UPMC we have a high risk breast and ovary program and we’re booked in to the summer already. So we would need to make sure that those mechanisms were in place that these people who we identify as having risk can get what they need to manage that risk.

And then we as genetic counselors need to kind of change our paradigm for counseling. So at the present we see people before we test and then talk to them after we test, sometimes they come back because they don’t want to test and they want to talk more and so we’ll be kind of reversing that. The testing will be done, mutation positive people with be identified and then they’ll be referred to talk about implications for them and their family. Then also I would imagine those families who the physician is concerned about because they have quite a bit of cancer in their family and we didn’t find anything that maybe we need to look a little bit further.

The other thing we have to think about is cost. Right now 3 site testing in the United States is about $500.00. The cheapest BRCA testing up until earlier this week was $1500.00 but most of the labs cost $2500.00 for sequencing and deletion duplication. And if we go to the traditional testing laboratory that’s $4000.00 so those are big costs that we have to think about that would probably need to come down before health insurers would be willing to jump on board. And so I said up until earlier this week and that’s because Color Genetics announced that they now have a saliva based test and a kit that they can send to your house that can test you for BRCA 1 and 2 for $249.00 and they won’t accept insurance. And so it begins.
What are some of the psychological costs? Overall most of the studies that have been done through the years have shown that there’s really no long standing anxiety or depression related to doing BRCA testing but there have been some qualitative methods that have shown that living with genetic risk affects people in subtle ways and burdensome ways. And so this is just an expert from an article that showed a woman who had previously tested positive for a mutation and had a mastectomy experienced rejection by previous boyfriends and she just goes on to say she’s had bad reactions, it’s hard for me to deal with so it’s hard for them to deal with, I don’t feel comfortable with it even after all these years so I stay alone. So I think that we need to recognize that although globally people are managing fine that there are more subtle ways that we have to potentially support them. And then also just recently a randomized controlled trial was done in the UK population based screening for Ashkenazi’s in the UK and with family history. So they took 1,600 people, did genetic counseling and consented about $1,000 of them, they divided them up into population based screening and family history screening. They were equal. Their demographics were very similar and they did testing for the 3 founder mutations. In the population based screening they found 13 carriers, 10 of those were family history negative, 3 family history positive. Then in the family history based arm they found 9 carriers. So I think that what we need to recognize is that in the UK the national health system has very different guidelines for screening and they are much more restrictive than our NCCN guidelines, even for people of Ashkenazi descent. So they look at first degree relatives, they don’t go further out, they look at only people diagnosed before 60 they don’t go at any age unless it’s ovary cancer, so some of the people in the population based screening who we see family history positive those were people who had a little bit more distant family member than the National Health System’s criteria would have captured. But basically what they found in this study which is the first
randomized controls trial of this kind, that 56% of the carriers that they identified did not meet the National Health Standard’s criteria for testing. They found a similar prevalence rate of carriers, about a 2.5% and this study is actually looking at some of those psychological outcomes from testing in this population. And they found on short term follow up that there were no significant differences between the family history group and the population based screening arm regarding anxiety, depression, health anxiety distress or quality of life. They are continuing to follow this group and they are also continuing to follow this group to see how identification of mutations has impacted health behaviors with regard to screening and prevention and more data will be coming in follow up.

The same group looked to see is it cost effective to do population based screening in the Ashkenazi population as compared to a family history based population and so these were their costs. So I just want to point out that first one, the cost of genetic testing 50 pounds so it’s maybe $70-$75.00 so much cheaper. Unfortunately I was unable to get my hands on specific numbers for the rest of these things like screening and surgery here, but their bottom line was population based screening for BRCA mutations is highly cost effective compared to family history approach in the Ashkenazi population.

What’s another consideration the benefit. We would identify women who had significant risk for breast and ovary cancer and I realize that my focus has been all on the women but men in those families would be at risk too and would be identified and potentially could benefit from additional screenings as well. And so this identification of these women may be able to prevent a significant number of cancers or maybe reduce mortality as a result of particularly ovary cancer.
So are we ready? Maybe. I think here we would need to have lower test costs before we could really put it into action. Particularly I think we would be more ready to start this in the Ashkenazi population because of the focused testing, because of the fact that in the Ashkenazi population there is a much more awareness about genetic testing due to the genetic testing that’s been happening for years. There are lots of systems for education and support available in the Jewish population and so I think that if we’re going to go for it that would be a good place to start and that it would spread from there. Do I think that it’s long before it becomes population based screening for everybody? Probably not just because of the sheer force that’s coming from the population as a whole to make it happen. And so I think we just need to probably get ready to embrace that and think about how we can best support our practitioners in that testing process.

And so here just sort of in closing, population based screening community study is happening currently at Einstein in New York in the Ashkenazi population they are recruiting people who are at least 25 years old, have one or more Ashkenazi Jewish grandparents and have not yet already undergone BRCA testing, and they’re offering testing for $100.00. So they brought that down a lot and I think it’s an attempt to see how it can work here.