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PART 2 – DEBATE: Is breast screening in patients over 70 cost effective

Dr Pagani: Good morning, everyone. Welcome back. After the very interesting session and discussion of yesterday afternoon, this morning we are moving to more clinical sessions and to start with, we decided, with Laura, to talk about screening in older patients. Is it cost-effective after 70 years? And we invited two very well-known breast radiologists involved in screening. One, and the first one, speaking in favor of extending the age of screening, is Dr van Ravesteyn from Rotterdam, the Netherlands, and the other one, who was forced to take over the opposite view, is Dr Panizza from Milan. They are there live, and we hope to have, as yesterday, a very live and interesting discussion afterwards. So, enjoy.

Dr van Ravesteyn: Thank you very much. I hope everyone can hear me. I see a nodding. Okay. So, indeed, I will be talking today about breast cancer screening in older women and whether it's cost-effective and I will argue that it is indeed cost-effective to screen women over the age of 70. So, I would like to start with a very broad overview of screening and the benefits and harms that it has been associated with. So, in contrast to treatments, screening is targeted to an asymptomatic population. So, it is targeted at a very large population of women without complaints, and it has a wide variety of harms and benefits. So, some of the harms apply to a large part of the population. For example, having some anxiety when getting an invitation, or when having a false positive screening test, then also, harms like undergoing the test itself. And then, on the other hand, screening has benefits, but those benefits are often only for a small population. So, for example, the most important benefit is a reduction in breast cancer mortality, but that only applies to a subgroup of the population undergoing screening. So, I would like to continue to look at the most important benefit, mortality reduction, for women aged 50 to 69-years-old. There have been a lot of trials actually looking at mammography screening and in all those trials, if you take them together, which has been done by, for example, the independent UK panel on breast cancer screening, you will find that overall mammography screening can reduce breast cancer mortality by around 20%, and some of those trials also included older women. So, if you look at the mortality reduction in older women specifically, it has been found that in those trials that included older women, the estimate is also that it can reduce breast cancer mortality by 20%, although, if you look at the confidence interval, it's quite wide, so that indicates that it's not statistically significant, the mortality reduction in older women. So, there's more uncertainty there. And that's also partly due because the trials were not powered specifically to find the mortality reduction in older women. Another way of looking at the evidence in older women is look at observational data. So, here I'll present a study from the Netherlands, in which we looked at the mortality, breast cancer mortality over time, but instead of looking at calendar time, we used the fac that screening was implemented in the Netherlands in different municipalities in different years. So, we set the year as zero for the year that screening was implemented in

a specific municipality. And this has the advantage that you sort of correct for a background trend. So, it might be that treatment is also reducing mortality, but if you said screening, the screening moment of screening implementation at moment zero, you sort of can look at the moment before and after screening in municipalities specifically. So, what we found was that before the start of screening, there was stable breast cancer mortality, a very small decline of .2% per year, but then after screening started, there was a 2%, almost 2% decrease in breast cancer mortality over time, which means that after 20 years after the introduction of screening first against the mortality was about 30% lower. What we then also did was look at the trends over time in older women specifically. I'm getting messages from the chat, so, I'll try to exit that. Sorry. So, I'll, so here we have the breast cancer mortality in women aged 75 to 79, 55 to 74, and 40 to 54. And what we actually found was that for older women as well, there was a significant reduction in breast cancer mortality after the introduction of screening, of about 34%. And what I like to point out is that the reduction started later in time, so, around six years after the introduction of screening, and that is mainly due to the fact that screening was extended to older ages in the Netherlands sometime after the implementation. So, the reduction started later, but it was actually steeper in older women than in, in women aged 50 to 69. So, there are several factors that can influence the benefits and harms in older women. So, women age 70 plus versus younger women. So, on the one hand, breast cancer incidence increases with age, so, there are more breast cancers to find, so, there can also be more breast cancer deaths that you might prevent with screening. At the same time, it has been shown that the screening test sensitivity is quite good in older women. So, it increases with age or at least it's as good as for women aged in their 60s. I think it's quite similar for women in their 70s and it is mainly due to lower breast density. So, younger women have very dense breasts and in older women, that is not the case. On the other hand, things that make the balance between benefits and harms less favorable in older women is mainly their lower remaining life expectancy. So, due to the fact that they might die from other causes sooner, there is a reduced potential to avert breast cancer deaths, and there are also fewer life years to be gained. And it also, because of the lower remaining life expectancy, there's a higher probability of over-diagnosis in older women compared to young women. So, just a few words on over-diagnosis because it's an issue that has been debated a lot. So, the definition of over-diagnosis is the detection of tumors that would not have been detected in a woman's lifetime in the absence of screening. And this might include non- or slowly-progressing preclinical cancers. It might also include regressing cancers. The difficulty is, which is also obvious from the definition, that it's often unknown what would have happened in the absence of screening. So, there's often no appropriate control group to compare the incidence with, once the screening program has been implemented. And therefore, the amount of over-diagnosis is largely unknown and widely debated. So, there have been wide ranges of estimates published from 0% to 54%, but most reliable estimates go up to around 10% of cancers that are diagnosed. And the general consensus is, however, that there's more over-diagnosis when screening older women. So, I would like to present one study that we did for the benefits and harms for older women. It was done in a setting in the United States and the study used three different microsimulation models. And we modeled biennial screening starting at age 50 with varying upper ages. So, the upper ages varied from 74, up to 96 years old. And what we got from the model were all kinds of benefits and harms. So, there are two different life histories depicted here. So, on the one hand, you can have a woman that is born. Then, at some point there's an onset of breast cancer. After some time, the cancer can get detectable by screening and when there's then a screening test the cancer can be diagnosed, then there's a certain lead time. So, time between the cancer would have been diagnosed in the absence of screening, and that it's now diagnosed. And again, when detecting a cancer by screening, it can lead to earlier diagnosis, better treatment options. And in the end, maybe, death from other causes instead of the breast cancer. So, then there are life years gained and breast cancer deaths averted. On the other hand, there can also be, or there will also be women that are over-diagnosed. So, for example, again, there's a life history here with someone being born, having an onset of cancer. Again, the cancer is detectable at screening, but here the cancer is diagnosed by screening, whereas there would not have been a diagnosis without screening. So, the woman, this woman still dies at the same moment in time from other causes. And now, she has breast cancer detected in her life through

screening, whereas without screening, she would have remained healthy up to her death. So, in this study, we looked at a range of benefits and harms, of which I will show a few. So, here are screening benefits by age. So, what you see on the Y axis here is the number of breast cancer deaths that are averted through screening, per thousand screens for the different upper ages. So, we started at age 74, 76, et cetera, up to age 96. And the three models are the three different lines. So, if you, for example, look at the middle line, you see that actually at around 80, there are still a substantial number of breast cancer deaths that are being averted, roughly the same as at age 70, but then, it starts to decrease with increasing age. And if you look at the number of life years gained, then you see actually a decrease after age 74, just because women have a lower remaining life expectancy when you avert one breast cancer death at age 74, you gain more life years than when you avert one breast cancer death at a later age, but still, there are benefits, although they become very small after age 90. If you then look at the screening harms, again, we looked at multiple harms, but I show two of them here. So, the number of false positive screens is actually quite stable per thousand screens. So, it remains almost stable, even up to age 96. But on the other hand, when you look at the number of over-diagnosed cancers, and we looked at both invasive and DCIS cancers, you see that there's a quite steep increase with increasing age. So, at age 74, it's around or ranging, again, here, you see the range, reflecting the uncertainty there is around over-diagnosis. So, it ranges between one to five, but then at older ages the range is, well, there's a clear increase and the range is now from 4 to almost 10, I think. So, what we then also did is try to make a summary of the benefits and harms by using QALYs. So, Quality Adjusted Life Years take into account both the benefits of having life years saved, but also, the harms of undergoing false positives and having an over-diagnosed cancer. So, what we then saw here is that if you look at the QALYs gained, they are quite substantial at age 74. So, they range from 7 to 10, but then, when age increases, screening, at some point, does no longer lead to QALYs gain. So, at age 90, actually, screening is no longer beneficial in terms of QALYs, but again, up to quite a high age, we still found QALYs being gained. And the other graph basically shows the same picture. But then, if you look at how much, what percentage are the life years gained reduced because you adjust for quality of life. And again, at age 90, all life years that you've gained are actually again lost, because women are over-diagnosed and being falsely referred for screening. In the study that I just showed, we did not look at cost-effectiveness of screening after age 70. There has been another study in the UK that looked at the cost-effectiveness of screening. So, the study was done in a UK setting. So, in the UK, they have a three-year interval, instead of, in most European countries, they have a two-year screening interval. This was also a modeling study and looked at upper ages from 72 to 90 years. So, here you see a graph again, showing the QALYs by increasing upper age. So, it looks quite similar as the graphs that I showed from the models on the previous slide. And again, at around age 90, it becomes no longer favorable to screen, because you lose too many QALYs. And in this study, they also did, went to step... they went one step further by looking at the costs and QALYs, and then in the end at the cost-effectiveness of screening. So, what you see is that with increasing upper, upper age, so, strategy 1 went up to 72-years and strategy 4 we went up to 81-years. So, with increasing upper age, there's an increase in treatment cost, and this is due to the increase in incidence with age, but also due to over-diagnosed, cancers that are being treated now. And there's a quite sharp decrease in life years in QALYs gained. And if you then do the cost-effectiveness analysis, that is making a balance between the costs and the QALYs, they actually found that screening was cost-effective up to age 78. So, there, they found that for each additional QALY that you would gain by screening, that QALY would cost you 15,000 pounds. And in the UK, often a threshold of 20,000 pounds is being used here for an intervention to be called cost-effective. So, screening can be cost-effective up to age 78. Again, this is also reflected in the recommendations from the EU, which now state on their website that for asymptomatic women aged 70 to 74, with an average risk of breast cancer, the guideline development group suggest mammography screening over no-mammography. However, if you look at the current screening practices in Europe, you still see that many countries end screening at age 69, rather than going up to 74. So, some countries go up to 74, including the Netherlands, some parts of Italy, Sweden, and France, but still, many countries stop screening at age 69 in Europe. So, if we go back to the factors that influence the benefits and harms in older women. So, the main drawback for screening older women is the

lower remaining life expectancy. However, recently, or already over a long period, there have been substantial increases in life expectancy over time in many countries. So, for example, if we look at the Dutch screening program that started in 1990 and since then life expectancy has increased for Dutch women by five years. So, I think it really makes sense to extend the upper age from 69 to 74 years in many countries. So, I would like to end with a few statements and then with a conclusion. So, I think it's really good that there is an upper age for breast cancer screening because screening older women is associated with more over-diagnosis and fewer life years gained. However, I think in many countries, the upper age is currently too low, because life expectancy has increased over time, and because it has been shown that screening can be cost-effective to age, maybe, 80 even. So, I think screening programs should be extended to include women aged 70 to 74. And for the future, I think that there can be a lot more done on looking at comorbidity or health or remaining life expectancy of any individual women to consider determining an individual or more personalized screening upper age in screening programs that are already moving towards a more individualized approach. So, with this, I would like to conclude, so, breast cancer screening is also effective in older women. However, due to the shorter life expectancy, the benefits become smaller and the harms increase, but despite this less favorable balance, it's still very cost-effective to screen women at least up to age 74 years, and probably also in many countries, maybe up to age 80. So, thank you very much. And with that, I would like to give the floor to the next speaker and also, I acknowledge the funders of the studies that were included here. Yes, and that's my group. I think we take questions after the next speaker, right, in the debate?

Dr Pagani: Yes. Yes.

Dr Panizza: Okay. Thank you for the invitation. And so, I have to answer to the question, is breast screening in patients over 70 cost-effective? I'm on the side of no, but we will see that it is something to discuss. I mean, it's impossible to say yes or no, and you will understand why. So, first of all, I want to remind you that we have the national system organized screening, that is a public health intervention, but we have also a spontaneous screening, that's a personal health intervention. There are differences in the two screenings, the first one is not tailored, doesn't take into account the personal breast cancer risk and the philosophy is "one fits all." So, it's the same for all the patients, it's paid by the national health system. The spontaneous one is tailored. It takes into consideration the breast cancer risk and use other techniques, mammography, but also, other techniques. Okay. About the harms, over-diagnosis is one of the most important harms, especially, in an old patient. And then, we have seen also the other. The next please. Okay. A few words about when to stop the screening, because the question was over 70, cost-effective, but as you have seen in the previous presentation, the breast screening is effective until 74, because the literature demonstrated it, as in this paper, there is a significant reduction in mortality in the 70-74-year-olds; next, and if you look at the guidelines for screening mammography among women 75-years and older, you see that in some society, they suggest to continue screening until 74-75. Next. It's... so I found this very interesting document. It's a recommendation from a National Italian Consensus Conference, from the 2007, that it recommends why to continue screening until 74. That's why, because it's difficult to say no before 75. That's why I'm trying to convince you... to show you why we have to continue to 74, because the sensitivity is the same, the expected specificity is the same, and there is a greater positive predictive value of screening and also, a lower cost per diagnosed cancer. There are also negative aspects, as participation in screening that tends to decrease with increasing age and the life, expectancy is lower. Next. Due to the limited life expectancy and competitive causes of mortality, the risk of over-diagnosis and over-treatment is substantially higher. But the decision to extend the organized screening beyond the age of 70 essentially depends on the local availability of resources and the life expectancy. And it's important to underline the important role of the family doctor, that is the only doctor able to calculate exactly the life expectancy of a single woman. In one of the indicators and parameters to take into consideration is the bone densitometry, which can predict the risk of bone fracture on osteoporotic basis. This is a frequent cause of death in elderly women. And then again, there is no evidence from controlled studies that is true, of effectiveness of screening over the age of 70, but it is

reasonable to expect the screening of over 70s to have the same or better diagnostic accuracy than 50 to 69-year-olds, as already demonstrated in the previous presentation. The next, please. So, they concluded that in case of sufficient availability of resources, it's recommended to extend the mammography screening program up to 74. And again, I think this is most important, that if the extension of the program is not possible, the alternative solution should still be so to allow women of the age group considered previously involved in the screening program not to fend for themselves, if they still wish to be followed by the same screening program. So, it's very important also the wish of the woman. Next, please. In conclusion, if the program is able and the cost-effectiveness analysis suggests that they extend the screening in 74 is maybe convenient, depends on the recurrent resources. And again, important is the family doctor in the decision to continue or not. Next, please. So, this is a paper from the previous doctor, who was Dr van Ravesteyn, again, in favor of the expanding of the screening until 74. Next. And then, look at this review, they observed something that is well known, that is why we are discussing about it, that there is a considerable uncertainty about the benefit of screening mammography in women aged 75-years and older, and the most guideline panels and organizations recommend decisions about screening mammography in older women be individualized, so tailored screening after 75. Next, please. And again, in this review, they estimated the late life of the screening, saying that the Gail model that we use in younger patients is not useful over 70; the advancing age is actually the major risk factor for breast cancer. And the incidence of breast cancers increases substantially with age in between ages 75 to 79. Next. Concerning the estimation of life expectancy, we know that while the risk of developing and dying from breast cancer increases with advancing age, it could be interesting to consider the screening, but we know that the life expectancy reduces the chances of dying for an asymptomatic screen-detectable cancer. And again, and age alone is a crude predictor of life expectancy. Next. So, the estimation of benefits, of the benefits and harms of screening in this group of women after 75. They find the benefit that is the reduction in mortality. And, again, the harm, the most important the over-diagnosis, yes, we have already seen. So, the two factors are reduction in mortality, the benefit and over-diagnosis is the harm. Again, thanks. The next, please. So, this is an interesting recent paper. Again, about the continuation of the screening and they demonstrated once more, in an eight-year breast cancer mortality evaluation, that with screening the 70, 74, we can... So, there is a difference, we can save one life, avoid one death per 1000 patients in screening the patients from 70 to 74. Next. But if we move to the 75 to 84, the risk difference is only as .07 deaths per 1000 patients, so, they concluded that continuing the annual breast cancer screening past 75 did not result in a substantial reduction in eight-year breast cancer mortality compared with stopping screening. This is... the reduced benefit is due to the competing causes of death. As you know, such as cardiovascular and neurologic condition, and there is an overtake of breast cancer mortality with increasing age. Next. So, again, the justification of annual mammography is that treatment is more effective for the small asymptomatic tumors detected at screening than for the larger symptomatic tumors detected in the absence of screening. But if we look at the kind of cancer found with… in the screening of the population, we found smaller cancer that became clinical, maybe, where it will not become clinically apparent in the absence of screening, but we found also aggressive asymptomatic tumors. Next, please. There is something to underline, and I found this in this paper, that if we look at screening the patients after 75, we see that the 36% of women with short life expectancies are still screened. And that suggested that we need a new intervention to further improve targeting of screening, according to life expectancy. So, we understood that a lot of patients are screened unusefully and that about 36% of patients after 75. Next. Concerning the breast cancer survivors, I found this interesting paper from the International Society of Geriatric Oncology. They recommend with this consensus to stop mammography for breast cancer survivors age 75 and older, if they are expected to live less than five years, consider stopping mammography for breast cancer survivors age 75 and older who are expected to live between 5 and 10 years, and continue mammography for breast cancer survivors aged 75 and older, who are expected to live more than 10 years. Next. To conclude, so, the national health system organized screening has to stop after 74. We have to move to a spontaneous informed screening that has to be tailored with the help of the family doctor, taking into consideration life expectancy, physical and psychological conditions, and woman preference. Next. But we

have to take into consideration, as underlined in this paper, that not only the reduction in mortality has to be considered, but, as you see in this example, that they talk about a patient who will die in five years, with or without screening for breast cancer. Two scenarios. In one case, she will die in her sleep thanks to the screening, in the other scenario she will die of painful metastatic breast cancer. So, we have to take into consideration also those, the quality of life, not only the reduction in mortality. Next. Another topic, interesting, is the decision aid. So, we have to help the patient to decide if to continue or not the screening after 75. This is a paper from the Harvard Medical School of Boston, and they recommend to inform the patient. And they demonstrated that informing the patient we can reduce the over-screening, as we have seen before. Next. They suggest in this paper-based mammography screening decision aid to help the patient to understand what they want to do. It's something very easy and fast, as you can very easily visualize the difference between the patients screened, on your left, the advantages and on your right, the patients who didn't undergo screening. So, there is one less woman out of 1000 may die of breast cancer, who chooses to have a mammogram, on your left. Next. This one is showing very well the over-diagnosis effect. Again, on the left, the patients undergoing screening. On the right, who stopped screening. And the next, please. And again, this is the effect on false positives, 100 false alarms concerning the patients who are undergoing screening, no alarms in the others. I think this is a good way to explain to the patients what is the effect. What are the advantages and the harms of the screening, to help patients to decide if continue to the screening or not. Thank you for the attention.

Dr Pagani: Thank you both. I think that you addressed very well the screen for the discussion. So, as mentioned before, I think that the age is determinant, and the age varies according to the country where you live. So, you mentioned several times the life expectancy, but this, of course, change a lot according to the country where you are from, and also, the proportion of older and younger people with breast cancer in different countries. So, I think that maybe you agree that we should continue up to 74 in countries where the incidence of breast cancer increases with age, and where there is a long life expectancy. In other countries where the life expectancy is shorter, and the proportion of breast cancer patients is more shifted to the younger age population, maybe the recommendation should be different. So maybe I would like you to first comment on that. Nicolien?

Dr van Ravesteyn: Yeah. Yes. I think that what you said all makes perfectly, perfect sense. So indeed, I think for each country, there is probably an optimal screening program, and in countries where the life expectancy is lower, then probably it's better to screen relatively young people instead of extending to older ages. Yeah. So, indeed you should take into account both the incidence level and the remaining life expectancy, or the... yeah, the life expectancy in a country specific.

Dr Pagani: Pietro, do you agree? You are mute.

Dr Panizza: Sorry. I'm a disaster today. Anyways.

Dr Pagani: Yes! I'm not asking what you did yesterday night.

Dr Panizza: I studied for the presentation. Anyway, so, I totally agree. So, if you have a good program working in the 50, 69 years, and you have enough resources, you can think about older patients, older women, also because it costs much less than move to the youngest, because we are talking also about 45 to 49 years. It's not the topic of today, but you have to take in consideration if you have money to spend, where to spend that money. But anyway, I agree there are big differences in the countries, but also, in the regions in Italy. So, the south and north have different results in the screening programs. So, it's up to the organizer to decide if they can move. So, expand the screening to the women older than 69 or not.

Dr Pagani: And I think that there is a question which I fully agree with, is that if you move to a tailored screening program, according to the life expectancy of an individual woman, the role of the GP is key. But we need to educate GPs, because I think that they're not ready, and I wonder if they will be ready in the next

future to screen and assess the life expectancy of the individual woman. So, I think that the risk also of the Boston approach is that the individualized and spontaneous screening will be offered only to women of a higher socioeconomic status, who do go for, to the gynecologist, to the GP routinely, but all the others, a very big part of the population, will be excluded. So, Pietro, first you, because you raised this.

Dr Panizza: Yes, I totally agree, and this is the problem. The good thing of the screening program is that to be equal to everybody, to all the society classes, and so on. And this... and this is true. So, I totally agree. I mean, the patients that are interested in checkup and so on, are the high-society, I mean, the patients who already go to the gynecologist, to the doctor, and so on, but we have to speak also the women that are not used to, for economical problems, for instance.

Dr Pagani: This is something to be, you know, for the advocates to be involved. They are not in the panel today, but I think this is a role for the advocates, to teach and to, also, older women to be screened and to be checked in some way. So, Nicolien, do you have another position on that, any?

Dr van Ravesteyn: No, so, I think there are several aspects here. So, one is indeed that offering or having a screening program really can reduce inequity, which I think is very important. On the other hand, if you want to target women with a certain life expectancy, you will be mainly reaching the higher socioeconomics classes, but then to say, okay, then we'll offer screening up to a very high age for everyone is also a bit, maybe not ethical, because then you are actually having a low socioeconomic group that you are offering screening, but then they actually only get mainly harms and not the benefits. So, that might seem equitable, but maybe it's not for them the right choice. So, it's a difficult issue, I think. That are making myself clear? But yeah, I think it has different aspects.

Dr Pagani: Pietro, would you like to comment or no?

Dr Panizza: No, I agree. So, I agree.

Dr Pagani: I think what I understood from your presentation is that maybe, according to, you know, on average, it would be worth expanding to 80, on average.

Dr van Ravesteyn: Yes. And so, I think there, it really depends on, on which country you are looking at. So, I think in some countries that might be considered, but to be honest, I think 74 is probably the right age for many, many European countries. If life expectancy will be increasing further, then, that might become a good option at some point for really programs. But on an individual level, there are still many women that are quite healthy at age 76, 78. So, maybe for some subgroups that would make sense to go up to, well, even a little bit higher than 74.

Dr Pagani: Yes. Then someone raises of course the issue of comorbidities, but these are part of the life expectancy calculation. Another very important topic that you touched, Pietro, and we discussed before we started, is the paper trying to... this is a slightly different topic, but the paper looking at the past breast cancer follow-up, showing that, if I recall correctly, that maybe also the annual mammography, which we prescribe after the diagnosis of breast cancer, the duration in the follow-up can be different according to the life expectancy. Can you maybe comment, because it, is a slightly different topic, but I think it's very important also to address this briefly.

Dr Panizza: Yes, so I found this paper from the Society of Geriatric Oncology that, so, I totally agree. I mean, you have to evaluate also the expectancy of life to decide which follow-up for every patient. This case, the tailoring is, is very important. So, this is not the problem that we have with the screening because they are already following-up those patients, and concerning the examination I think, they are not different from younger patients. So...

Dr Pagani: Yeah. So, maybe, Nicolien, do you have any idea, comment, or?

Dr van Ravesteyn: No, not really. So, to be honest, I don't know the details of that paper, but I think it relates to the same issues, being, how long do people still have the time to be able to benefit from the either screening or extra surveillance? Yeah, no, so, I agree that it's an important other way to look at it.

Dr Pagani: And then a very, I think a very short comment on one question on MRI in screening of older patients with less dense breasts, very short comment. Is there any role for MRI in screening older women, in general?

Dr Panizza: Sure. There is a wonderful study from Netherlands concerning the patients with high-risk, but it's a different topic, demonstrating that also on the dense breast now there is a... so I was thinking of dense breast and not high-risk. And they demonstrated that it is very useful, it's much better and much, so, performing and much better than mammography, but I think it doesn't have any sense in older patients, older than 70, 75. Also because it is a difficult examination to perform in a patient so old, I mean. But, it's something to say that always people think that in the oldest patients, there is not a problem of dense breast, it does exist, because when it's fibrotic is always dense, doesn't change with menopausal... menopause. But I don't consider MRI the right... an examination to use after 65, 70, yes.

Dr Pagani: Do you agree, Nicolien?

Dr van Ravesteyn: Yes. Yes, I totally agree. I think MRI has indeed been shown to be very good for women with dense breasts, for younger women. But I think if you start using it in older women, you will also, again, probably find much more small cancers that might not be relevant to find, so, it will probably also increase over-diagnosis a lot, which is another reason, apart from the less dense breasts, to not use it. And of course, the very much higher costs, still.

Dr Panizza: And do not forget that now we have the CESM, the mammography contrast medium injections. So, maybe in the future, we could consider that, that is something more easy to use and more comfortable for the patients also.

Dr Pagani: Okay. So, Laura, do you want to make any comment, something I forgot?

Dr Biganzoli: No, you did very well, the only issue is that if you compare what we said yesterday, to what we are saying for screening, is clearly there are two different dimensions. Yesterday we spoke about the relative importance of giving an age to an older patient because, you know, what is important is not the chronological age, but it's the performance of the patient. I do understand that in a screening program that is organized by a national health system, you have to put an age-cutoff, but this makes things very problematic, because I guess that none of the papers have been presented today, when evaluating the cost-effectiveness of screening in elderly patients, corrected the analysis based on the health status of the patients. So, it's just, you know, a median evaluation of the performance of this screening in the older population that doesn't account, take into account the extreme heterogeneity of the population, namely also in the 70, 74 age range, you may find unfit patients who are not going to benefit from screening, while you'll have a lot of older patients, 75 plus to 80, that are perfectly fit to have a life expectancy between 12 to 15 years. And they're going to, my opinion, to benefit from a screening program. So, I guess we will have to start introducing all this variability, while deciding how to go on with screening above a certain age. So, we cannot longer continue to discuss if I go up one year, two years, three years, no, this this not the point, the point is, which is the fitness of the patient? So, we have to try to move on in our thinking, or better tailor older patients with screening programs.

Dr Pagani: Okay. So, I hope I asked all the questions which were sent. So, I think that we will go straight to the treatment part. So, I pass the micro to Laura and thank you, both of you, for the very good presentations and discussion.