

Kristy Colvin IMDSA President: I would like to introduce you all to Dr. Colleen Jackson-Cook. She heads the MDS research at Virginia Commonwealth University in Richmond, Virginia. We are all so excited that you have taken the time to visit with us Dr. Jackson-Cook.

Q. *Michelle Easterly National Vice President:* Do you see any hope in the gene therapy direction with kids with Down syndrome with MDS?

A. *Dr. Jackson-Cook:* Gene therapy is a hard area to address for MDS or Down syndrome in general. As we learn more about the causes of these conditions I think there may be some aspects that could be helped with therapies of different types. However, there are other aspects that are unlikely to be helped since the situation will exist before the child is born.

Q. *Michelle Easterly National Vice President:* what if any are the odds of someone having a second child with MDS or Down syndrome?

Q. *Irene Gunnels Membership Chair:* Do you find a higher incidence of miscarriage with families with Down syndrome/MDS?

A. *Dr. Jackson-Cook:* This is a good question. For some families there is an increase frequency, but others do not show this. In general couples who have a child with t21 have a 1percent risk for having a 2nd child with Down syndrome. Since the number of families having a child with MDS is much less the figures for recurrence that are specific to MDS are not as strong. Nonetheless, since many cases of MDS have the same chromosome sorting problem as Down syndrome one could anticipate this risk to be similar. Michelle, I hope this also addresses your related question.

Q. *Irene Gunnels Membership Chair:* This makes sense we have four "normal" children and we lost four others due to miscarriage.

A. *Dr. Jackson-Cook:* Irene, I am sorry to hear of your loss. I had two pregnancy losses myself. One thing that might be of help is to have chromosome testing done and genetic counseling can be helpful to some couples.

Q. *Michelle Easterly National Vice President:* Have you ever heard of a child having two gene disorders? My son has MDS and XYY.

A. *Dr. Jackson-Cook:* Yes. The co-occurrence of Down syndrome or less commonly MDS has been observed along with sex chromosome findings in several families. These tend to be the most commonly seen conditions because they have the highest frequencies of occurrence and by chance may arise together. We have done studies with some families having a child with t21 and a sex chromosome condition and have found that in some case they were related and in others were chance events.

Q. *Michelle Easterly National Vice President:* Wow I had no idea!

Q. *John O'Brien:* Our son has 20% mosaicism and a small ASD. Is there anything known about the rate of spontaneous secundum ASD closures in Down syndrome or MDS?

A. *Dr. Jackson-Cook:* I am not a clinician and so, without medical info that is specific for you child I would not feel comfortable answer this. I do not want to provide any misleading info and just am too limited to answer this accurately. I am sorry.

Q. *Tina Jordan:* How frequently does the percent of affected cells decrease as the person gets older?

A. *Dr. Jackson-Cook:* The observation of a decrease in the percent when blood cells are studied has been seen fairly often (no firm figures on this, but we are working on coming up with them) the blood cells divide often and so they are thought to show many other cell types to date, there has not been any correlation in clinical outcome that has been associated with this change in percent but as people with MDS age we are hoping to learn more.

Q. *Cynthia Jones:* I never knew the percentage of affected cells could change I have learned something tonight!

Q. *Nancy Ross:* When you say no correlation in clinical outcome you mean no functional changes?

A. *Dr. Jackson-Cook:* Yes to date there has been no clear association in the improvement or poorer progress that has been linked to a decrease or increase in the trisomy cell line percent. One area of study on this topic has been for people who develop Alzheimer's like traits as they age however so far there is not a correlation with outcome... at this point it just seems to be selection for cell line that divides most rapidly. Since the brain cells do not divide this change would not be expected to influence developmental abilities.

Q. *John O'Brien:* Is there any correlation between blood mosaicism and mosaicism measure in any other tissue?

A. *Dr. Jackson-Cook:* This is a great question and one that we are actively trying to understand. There can be differences in the percent of cells showing trisomy between different tissues. In our study we have a trend toward a higher # in his cheek rubbings compared to blood samples. However, this is not the case for all individuals.

Q. *Cynthia Jones:* Why the higher percent ages in the cheek cells than the blood samples?

A. *Dr. Jackson-Cook:* We are not certain. It may reflect a difference in his number of cell divisions with the blood cells having more division and hence a greater chance to select against the trisomic cells. It is also possible that the percent may actually be different between different tissues as a result of when the error occurred that gave rise to the mosaicism. Early in embryogenesis the brain and buccal mucosa cells (cheek) have a common cell type origin this is why we are very interested to better understand this finding.

Q. *Tina Jordan:* Can you explain the idea that the percent doesn't matter as much as where the affected cells are located?

A. *Dr. Jackson-Cook:* I'm not sure I understand the question, but I think what is being asked is based on the location of t21 cells for example if the brain cells have a high or low frequency one may show a more severe or less severe outcome we really have no data to know this what we do know is from anecdotal cases. for example a child has been reported who had a heart problem that was consistent with Down syndrome but had no other finding at there time of surgery cells were taken for chromosome studies and the here was shone to be comprised of mostly 21 cells but no other tissues had a high percent of 21 cells from this case it has been suggested that if a tissue is more or less affected that could impact the phenotype

Q. *John O'Brien:* Do you have an idea of what percent of MDS is cause by rescue versus a late non disjunction?

A. *Dr. Jackson-Cook:* John, very good question. based on the families that we have studied so far it appears that about 75 percent of them are trisomy rescue (a meiotic chromosome problem followed by a 2nd mitotic problem the remaining 25 percent appear to be a mitotic sorting problem

Q. *Cynthia Jones:* so you're saying that the stage of development of the embryo when the MDS occurs determine which body systems will be affected or most affected.

A. *Dr. Jackson-Cook:* yes the timing of the chromosome sorting problem can influence which tissues are affected and the percent

Q. *Irene Gunnels Membership Chair:* refresh me on meiosis and mitosis

A. *Dr. Jackson-Cook:* Meiosis is the cell division process that occurs in eggs or sperm in typical meiosis division a single copy of chromosome 21 is placed into an egg or sperm. if there is a sorting problem then 2 copies can be included once fertilization happens. A total of three chromosomes 21 can be present. This may then be followed by a second sorting problem in the embryo. This type of cell division once there is an embryo is called mitosis the second sorting problem can result in the extra chromosome 21 being lost from the cell thereby giving rise to the mosaicism some cells with three chromosome 21's and some with two chromosome 21.

Q. *John O'Brien:* Does this affect the likelihood of having a 2nd child with MDS.

A. *Dr. Jackson-Cook:* Yes, this may influence recurrence risk in that families having meiotic error and a mitotic error may have a risk of one percent like families having child with Down syndrome. Those having a mitotic error and no meiosis error may have elsewhere risk we do not know for certain yet but it seems to hold so far.

Q. *John O'Brien:* Is there any easy way to tell if a child's MDS is due to a rescue of a meiotic problem or a later mitotic event?

A. *Dr. Jackson-Cook:* Not an easy way. What we are doing is looking at markers in the child and the parents and sibs when available and learning when the errors occurred we are also trying to identify if there are other changes in the meiosis process that are different and if these can be used to provide more accurate info to families for risk counseling

Q. *John O'Brien:* Thanks, we thought it would not be simple but we were curious

Q. *Tina Jordan:* Are siblings ever at a higher risk of producing a child with MDS?

A. *Dr. Jackson-Cook:* Great question for the most part no however there have been rare cases where more than one person having MDS has been born between generations at this time we don't have any accurate way to predict who may or may not have an increased risk this is another long range goal of our research

Q. *Tina Jordan:* If we haven't had a cheek swab done yet do you recommend it:

A. *Dr. Jackson-Cook:* Tina, the choice is really up to you at this time we do not have any clear predictive abilities that are linked to the test so there is nothing that you would change clinically or any different therapies that would be recommended

Q. *Nancy Ross:* how common is it for siblings to both have Down syndrome children?

A. *Dr. Jackson-Cook:* We have identified 12 families of this type either sib or parent and child and are trying to learn why these people have more than one affected individual in family. In some of the family the chromosome sorting problem happened in the related individual in other the chromosome sorting problems actually happened in the egg or sperm of the unrelated individual as so they were just chance events.

Q. *Cynthia Jones:* how likely is it for a person with MDS to have a child with MDS?

A. *Dr. Jackson-Cook:* As for the risk to a female having child with MDS this is hard. for a female who has Down syndrome in every cell the risk would be 50percent basically the risk is one half of what ever the proportion of egg cells having trisomy is we cannot know this value so the predication is very difficult but no higher than 50percent to date there has not been a case confirmed of paternity for male with full tr21 these males are infertile however form MDS this may be less straightforward one could look to see if the male is producing sperm but getting a young man with MDS to ejaculate into a cup for this study is a very sensitive and difficult takes.

Q. *Cynthia Jones:* Is there any documented cases of male with MDS father a child? Are males with Down syndrome sterile?

A. *Dr. Jackson-Cook:* I am not aware of any cases of full tr21 that have stood up to paternity testing that does not mean it cannot happen for a male with MDS in males with Down syndrome they do not produce sperm I do not know of any fertile males with MDS but if the percent of t21 cells is low enough in sperm it might allow for it to occur

Q. *Nancy Ross:* will you be coming to the conference

A. *Dr. Jackson-Cook:* Yes! How many of you will be there

A. Most everyone confirmed they would attend the conference.

Kristy Colvin IMDSA President: Thank you to Dr. Jackson-Cook for taking time to speak with us tonight. We look forward to seeing you at our 2nd annual conference and hearing more about MDS.