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| Title | Contemporary live birth prevalence of recurrent 22q11.2 deletions: a cross-sectional analysis from population-based newborn screening |
| Authors | Christina Blagojevic BMSc, Tracy Heung MA, Mylene Theriault MSc, Aoy Tomita-Mitchell PhD, Pranesh Chakraborty, Kristin Kernohan PhD, Dennis E. Bulman PhD, Anne S. Bassett MD |
| **Reviewer 1** | Dr. Roger Thomas |
| Institution | University of Calgary, Calgary, Alta. |
| General comments (author response in bold) | This is an excellent carefully performed and documented article.<br>**We thank Dr. Thomas for his kind words about our study.**<br><br>To place the problem in context, please provide a summary table of the frequency of other significant pathognomic deletions and other chromosomal problems.<br>**We have now included a new Table 2 with the prevalence estimates for well-known aneuploidies (trisomy 21, 13, 18) as well as several conditions that are currently included in the Newborn Screening program in Ontario (severe combined immunodeficiency, congenital hypothyroidism, cystic fibrosis, and phenylketonuria). With respect to the conditions included in the Table, the prevalence of the 22q11.2 microdeletion detected in this study is greater than all but Trisomy 21, highlighting that this is a relatively common rare disorder.**<br>**We have now modified our introductory statement in the Interpretation section to refer to this new table and its contents, as follows: "For context, comparable prevalence estimates using data from Canada and the United States for other genetic disorders (e.g., cystic fibrosis) are provided in Table 2; of these, only Down syndrome is more common than 22q11.2DS." (pg.10)**<br><br>Sample<br>Your sample of 30,074 anonymised blood spot samples from January 2017 to Sept 2018 comprises 11.2% of Ontario newborns and includes 26,448 singleton births and you identified 13 cases. Based on the newborn population of Ontario, what is the generalisability of your results?<br>**As suggested, in order to frame our results with respect to the overall number of annual live births in Ontario, we have now stated in the Interpretation: "Extrapolating results to the ~140,000 live births annually in Ontario,[22] one would expect about 66 births with a 22q11.2 deletion per year." (pg.10)**<br><br>Future directions<br>Please expand your statement about future directions you would advocate. What would be the cost of your overall envisioned programme and the costs/newborn?<br>**As per other recommendations above, we have removed the Future directions as a section. However, in the Interpretation (pg. 12) we have now expanded on our statement supporting genetically-based newborn screening for 22q11.2 deletions by drawing attention to universal criteria that often must be met for inclusion into a newborn screening program, one of which includes low cost. The decision to include the 22q11.2 microdeletion in newborn screening programs would likely include a thorough cost-benefit analysis. We do however note that the cost of screening for other conditions, such as for cystic fibrosis, is generally in the range of a few** |

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| | **dollars per sample: "For any such proposal, costs per newborn for NBS must be low, e.g. less than US$7 per sample,[30] methods must be scalable within current clinical NBS labs, and there need to be feasible plans for confirmatory studies and clinical referral for confirmed positive screening results.[31]"** |
| **Reviewer 2** | Dr. Sarah Dyack |
| Institution | Dalhousie University, Halifax, NS |
| General comments (author response in bold) | Great work. Very interesting.<br>Note good background, clear question, proper design for this kind of study, and in enough detail. No flaws that are important. Relevant to those in NBS implementation and administration, genetics, pediatrics, and neonatology. Also to public health/government.<br>Wish you were allowed to have more data points, as you have shown some unexpected results, including lower maternal age for a common microdeletion, on average more lower birthweight babies and confirmed that they have on an unbiased population basis, more complicated feeding problems than other infants.<br>A 10% sample of the NBSs is an appropriate sample size for this kind of study although I appreciate that more is better but balancing the costs also crucial.<br>Looking forward to your next publication on this topic.<br>**We thank Dr. Dyack for her positive comments and encouragement. We have now further emphasized the finding about lower maternal age in the Interpretation section (pg. 14).** |