CISNET Project Proposal

Cervical Screening in Women with Down Syndrome

May 2023

Specific Aims

This project aims to assess the benefits and harms of current cervical screening recommendations for the population of women with Down Syndrome in the U.S. and to evaluate the benefits and harms of a range of potential new screening strategies. Ultimately, it is hoped that the modelled analysis will inform future U.S. guidelines, and also inform policy making in the U.S. and in other countries.

The specific aims of this project will be:

1. To systematically review the literature to identify and synthesize available data on age-specific HPV incidence/prevalence, HPV vaccination, screening participation, rates of high grade precancer, and rates of cervical cancer incidence and mortality in women with Down syndrome in the U.S and globally (it is likely that data and information will be limited in some areas particularly around HPV infection rates, the advisory group will assist in understanding emerging data sources);
2. To use these findings to support an experienced modelling team to adapt and calibrate a comprehensive, pre-existing modelling platform of HPV infection and cervical cancer carcinogenesis (*Policy1-Cervix*) for a population of women with Down syndrome in the U.S.;
3. To configure an expert and consumer reference group to guide the discussions and evaluations performed;
4. With guidance from the reference group, to perform a wider survey of Down syndrome women and clinician concerns, challenges and preferences in relation to cervical screening; and
5. Taking all of the above inputs into account, collaborate with an experienced modelling team to use the modelling platform to evaluate the benefits and harms of current cervical screening policies recommended in the U.S. for women with Down Syndrome, and to consider a range of alternative options for screening in that may inform future guidelines for this group of women.
6. Going forward, it will be possible to explicitly adapt the model to directly inform decision-making in other countries (such as Australia) and this will be considered as a potential extension to the work (time permitting).

Research Strategy

Background

Individuals with Down syndrome have a lower incidence of most solid organ cancers than the general population, and they also have a lower life expectancy. Therefore, the tradeoffs between the benefits to harms of cancer screening may differ in this population, and optimal screening recommendations may not be the same as in the general population. For example, a CISNET-sponsored evaluation of the harm/benefit ratios for various mammography screening strategies in women with Down syndrome found that these are not as favorable as those for average-risk women and that the benefit of screening mammography for women with Down syndrome is less pronounced due to lower breast cancer risk and shorter life expectancy.[1]

Cervical screening has been established for many years in most high-income countries. Currently, many countries have transitioned, or are transitioning, to using primary high-risk human papillomavirus (HPV) HPV screening, which is a highly sensitive test for the molecular presence of the virus which causes cervical cancer and thus provides longer-interval protection than traditional cytology screening ('Pap smears').[2,3,4] In the U.S., screening every 3 years with cytology is recommended starting at age 21 years, with an option to either continue with cytology every 3 years over age 30 years, or to switch to primary HPV screening at 5 years, or cytology and HPV co-testing every 5 years, from age 30.[5] Screening is recommended to cease at age 65 years, provided there is no history of cervical abnormalities in the past 10 to 20 years and that the woman has screened regularly for this time.

Although widespread cervical screening has resulted in a substantial reduction in cervical cancers over the past few decades, there are notable harms that come with unnecessary screening. These include, but are not limited to, the discomfort of undergoing a clinician-led speculum examination for the collection of cervical tissue, the psychosocial impact of receiving an abnormal screening result and being referred for colposcopy, and the process of undergoing precancer treatment. There is some evidence to suggest that treatment may adversely affect obstetric outcomes in a small proportion of women[6] (although this may not be applicable to most women with Down syndrome). The harms and risks are likely to be even more pronounced in women with intellectual disability, as general anesthesia may be required for the collection of cervical samples for primary screening, and would be required for further diagnostic procedures; however, these potential harms have not been explicitly captured in previous evaluations of cervical screening guidelines in USA. When considering women with Down syndrome, the life expectancy of women is considerably reduced (by about 20 years), and so the benefits of screening particularly at later ages may be lower than the benefits for the general population of women. There is also evidence to suggest that women with Down syndrome are at lower risk of HPV infection and cervical cancer, given lower levels of sexual activity, which could further reduce the benefits that this group would obtain from screening. On the other hand, there are concerns about higher rates of sexual abuse for women with disabilities. Overall, studies have shown that women with disabilities have reduced access to preventative services and it is critical that screening is appropriately evaluated and prioritized for this group of women.

Cervical screening is one pillar of a triple-intervention strategy to achieve cervical cancer elimination (defined as rates <4/100000 woman-years), for which the World Health Organization has specified scale-up targets for prophylactic HPV vaccination, cervical screening, and cervical precancer and cancer treatment access and uptake. Previous CISNET whole-of-population modelling, accounting for prior and current U.S. vaccination and screening coverage rates, has estimated that the U.S. is on track to eliminate cervical cancer

as a public health problem in the next two to three decades, but that time to elimination could be expedited by 10-13 years by achieving higher screening coverage. [7] Increasing screening in under-screened and under-vaccinated women remains key to achieving cervical cancer elimination for all women and is a prime consideration in achieving equity in outcomes. However, in the case of women with Down syndrome, it is not clear that it is appropriate to recommend the same screening regimes as for other women, nor is it known whether the benefits-to-harms tradeoffs would be favorable in this population.

These issues and tradeoffs can be formally considered using a modelling approach, which will quantify the benefits and harms of difference approaches to cervical cancer screening in women with Down's Syndrome.

Location and approach

The project will be run as part of the National Cancer Institute's CISNET-Cervical program of work (currently in its second round of funding). The CISNET-Cervical consists of five modeling groups and a coordinating center at Harvard University (coordinating center PI, Dr Jane Kim). One of the participating teams is based at the Daffodil Centre, A Joint Venture between Cancer Council NSW and the University of Sydney, Australia (center PI, Prof Karen Canfell).

This project will be offered as a PhD project based at the Daffodil Centre under the supervision of Prof Canfell with co-supervision from Daffodil Centre CISNET-involved investigators (A/Prof Megan Smith, Dr Kate Simms and Clinical Professor Deborah Bateson), and close involvement from clinical experts Dr Barry Martin, Dr Brian Chicoine, Dr Kathleen Nolan, Dr Kirstin Jensen, and Dr Jason Woodward. There will also be a wider expert and consumer reference group (as above) which will be drawn upon for insights into the experience of women living with Down Syndrome.

The modelled evaluation will use the established and well-validated platform, *Policy1-Cervix*, developed by a team of researchers now based at the Daffodil Centre, University of Sydney, a Joint Venture with Cancer Council NSW, Australia. The model platform is an extensively validated model of HPV transmission, the development of cervical precancer and invasive cancer, and HPV vaccination, screening, precancer and cancer diagnosis, and treatment, and has been used for a variety of evaluations in the USA [7,8,9] and in many other countries, including global modelling for the World Health Organization's eliminations strategy and cervical screening guidelines.

A 3 year fully funded local scholarship of approximately $40,625 AUD per annum will be offered. The PhD position will be advertised through the University of Sydney, and we will seek a qualified candidate with skills and experience in epidemiology and an interest in qualitative analysis. The successful candidate will be required to undertake a systematic review of current evidence, conduct qualitative research, and will collaborate closely with the highly experienced modelling team at the Daffodil Centre, who will update the existing U.S *Policy1-Cervix* platform to model sub-population evaluations of cervical cancer prevention for women living with Down Syndrome in The U.S.

It is hoped that the PhD student could commence in research periods 3 or 4 2023.

It is envisaged that regular teleconference calls would be conducted with the U.S. investigators.

Investigators/Supervisors

Supervisors:

Prof Karen Canfell, A/Prof Megan Smith, Dr Kate Simms and Clinical Prof Deborah Bateson

Advisory Group Core Members:

Dr Barry Martin, Assistant Professor, Division of General Internal Medicine, University of Colorado

Dr Kate Nolan, Nurse Practitioner, Division of Gynecologic Oncology/The KIND Clinic

Dr Brian Chicoine, Medical Director, Advocate Medical Group Adult Down Syndrome Center, Faculty, Advocate Lutheran General Hospital Family Medicine Residency

Dr Jason Woodward, Associate Professor of Pediatrics, University of Cincinnati College of Medicine Division of Developmental and Behavioural Pediatrics, Division of Adolescent and Transition Medicine, Cincinnati Children's Hospital Medical Center

Dr Kristin Jensen, Associate Professor, Departments of Pediatrics and Internal Medicine, University of Colorado School of Medicine

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Summary

This research project aims to assess the benefits and harms of current cervical screening recommendations for the population of women with Down Syndrome in the U.S. and to evaluate the benefits and harms of a range of potential new screening strategies. Ultimately, it is hoped that the modelled analysis will inform future U.S. guidelines, and also inform policy-making in the U.S. and in other countries. The project will be undertaken as a PhD project, we are seeking a candidate with skills in epidemiology and an interest in undertaking qualitative analysis. The successful candidate will be required to undertake a systematic review of evidence, conduct qualitative research, and will collaborate closely with the highly experienced modelling team at the Daffodil Centre, who will update the existing U.S *Policy1-Cervix* platform. A programing background would be advantageous, but is not a requirement.

Addendum: About the Daffodil Centre

The Daffodil Centre is a joint venture between Cancer Council NSW and the University of Sydney, combining the complementary strengths of the two partners to accelerate progress towards our common goal of a cancer-free future. The Daffodil Centre is a leading research center on cancer control and policy – providing timely and relevant evidence to national and international policy-makers to inform best-practice decision-making in cancer control. We are focused on reducing the incidence, morbidity and mortality associated with cancer and on improving the quality of life of people with a cancer diagnosis. The Cervix and HPV Stream within the Daffodil Centre continues to make a significant contribution to both national and international policy development for cervical cancer control. The team's work spans modelling, observational epidemiology, clinical trials, and data analysis to create a template for how multiple evidence-based interventions can combine to form a roadmap for a cancer free future. The team co-leads the NHMRC Centre of Research Excellence in Cervical Cancer Control (C4), the large-scale Compass trial, and is part of the COVID and Cancer Global Modelling Consortium, supporting decision makers on decisions around screening and vaccination during and after the pandemic, and is a part of the CISNET-Cervical group.

Addendum: About *Policy1-Cervix*

The model platform known as '*Policy1-Cervix*' is an extensively validated dynamic model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis and treatment. The model has been used to perform evaluations in the U.S. and on behalf of national cervical screening programs in Australia, New Zealand and England relating to changes in screening technology, screening interval and screening management and their effect on costs, health outcomes, and resource utilization. These evaluations include assessing the impact of test-of-cure management in women after treatment for CIN2/3, evaluating primary HPV testing versus cytology, evaluating triage management options for HPV positive women, and estimating the transitional fluctuations in health outcomes and resource use for countries transitioning to longer-interval HPV testing. The model has also been used for a number of HPV vaccine evaluations, including effectiveness and cost-effectiveness of HPV vaccination in both girls and boys, taking into account catch-up vaccination, as well as the effectiveness and cost-effectiveness of the next generation nonavalent vaccine. It has also been used to evaluate the effectiveness and cost-effectiveness of screening and vaccination in both rural and urban China, Urban and rural Vietnam as well as the potential impact of screening and HPV vaccination on a global scale. The model is currently being expanded to account for different natural history for HIV positive women

through the development of an HIV-HPV model platform. We are the modelling group supporting WHO in the development of new cervical screening guidelines and previously co-led elimination modelling for WHO.