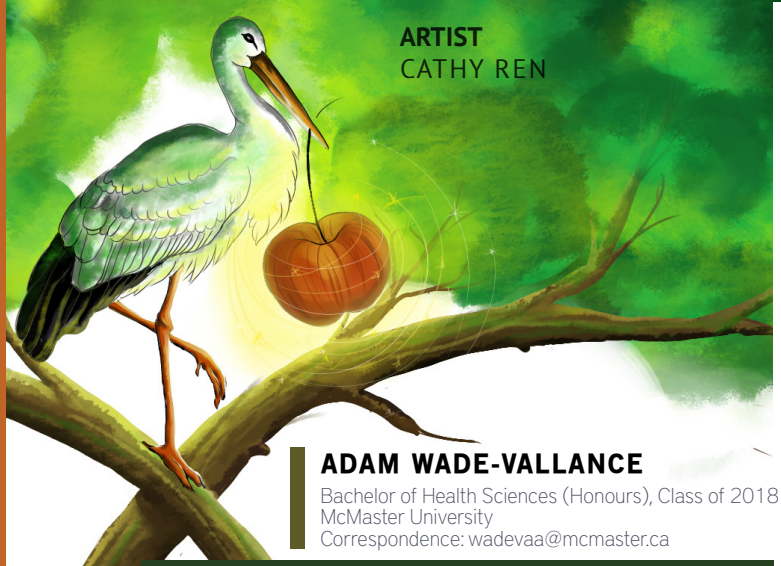
Newborn Screening and Whole Genome Sequencing:

A PERFECT MATCH OR AN EMERGING ETHICAL CRISIS?



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ABSTRACT
Canadian newborn screening (NBS) programs are successful in improving the prognosis of many affected neonates with early-onset disorders by enabling rapid diagnosis and treatment. However, many problems still exist with NBS programs including inconsistent coverage across provinces or territories, gaps in disease screening, and variable testing methodologies. Whole-genome sequencing (WGS) represents an increasingly cost-effective means of screening all genetic conditions with a single primary assay. Many benefits of WGS have been cited, including the ability to determine the exact causative mutation of a condition which could enable targeted therapy. Despite this, WGS in NBS carries serious ethical ramifications pertaining to disclosure of results, storage of data, and future development in NBS programs. Due to these factors, we are as-of-yet unprepared to incorporate WGS into Canadian NBS programs.

Newborn screening (NBS) identifies treatable disorders in neonates through systematic testing.[1-3] Upon diagnosis, prompt medical interventions can improve or manage the baby's health.[1-3] A disorder can be effectively screened if it is acute-onset, treatable, and has a simple and accurate diagnostic test. These factors have been enshrined in stringent requirements governing the incorporation of additional disorders into NBS programs.[1,4,5]

The expansion of NBS in Canada has spurred initiatives to develop assays which screen for multiple disorders simultaneously.[2,3] Despite this advancement, NBS remains sub-optimal, with high false-positive rates requiring cumbersome re-testing and follow-up.[6] Furthermore, coverage of disorders in Canadian NBS is disjointed as each province or territory coordinates its own NBS program.[7-9] Although these programs are constantly advancing with ongoing studies assessing screening accuracy and benefits, a standardized technique such as whole-genome sequencing (WGS) might streamline the expansion and regulation of NBS.[7-9]

WGS identifies all six-billion base pairs in the human genome, giving it the capacity to diagnose any genetic disorder.[6] In recent history, WGS has assumed a greater role in diagnosis and research due to dramatic cost reductions. The human genome project (1990-2003), developed the first reference sequence and cost a whopping 2.7 billion dollars.[10] This cost plummeted to just $4000 in mid-2015, and presently, the cost has dropped down to $1000.[3,10,11] Many scientists predict that costs will continue to drop, making WGS in NBS feasible in the future.[3,10-11]

Bodian et al. investigated the utility of WGS in a cohort of ~1700 neonates and found that WGS-based and conventional NBS diagnosis were highly concurrent.[6] Additionally, WGS gave fewer false-positives, resolved inconclusive results, identified causative mutations, and required fewer sample collections from preterm infants.[6] In some cases, it even detected nuances distinguishing closely-related conditions indistinguishable by conventional NBS.[6] Although findings like these fuel excitement for WGS in NBS, its problem and promise remain one and the same; it would screen all genetic disorders, regardless of any NBS list.[3] From this, an ethical quagmire arises that we are not yet prepared to face.[3,11,12]

Disclosure of sequencing results represents one serious issue. NBS is designed to uncover actionable findings, whereas WGS would screen everything.[4,5,11] For example, Huntington's Disease is not screened by conventional NBS because it is not a childhood-onset disorder and lacks effective treatments. WGS, however, would detect the causative mutation. Informed children could mould their priorities to a diminished lifespan and

would be spared a devastating mid-life diagnosis. Yet, if uninformed, they would mature free from this mental burden. Many argue inaction, the status quo in conventional NBS, is preferable.[11] This issue is compounded by the fact that WGS would uncover variants of uncertain significance or likely pathogenicity in every neonate, even healthy ones. Informing parents of these variants could cause needless anxiety, and confirming results would be expensive and time-consuming.

Another important concern is data storage and usage.[11] NBS samples are kept only short-term to enable re-testing, because babies cannot provide informed consent.[11-14] Parental consent is either deemed implied or unnecessary, and no Canadian province requires explicit consent.[11,13,14] Long-term data storage, however, does require explicit consent, as American lawsuits have demonstrated.[9] WGS would unearth information relevant to adult-onset disorders conditions. This would exacerbate storage issues as there would be medical reason to retain information for the baby's adulthood, but no consensual basis to do so. The current 'don't ask don't tell' philosophy would therefore be insufficient to inform WGS data management.[2-4,12]

Furthermore, there exist privacy concerns and the potential for abuse of sequencing results by third parties.[11] Insurance corporations that crave knowledge of a person's predisposition to disease when determining life insurance premiums may seek to take advantage of such information, and saboteurs could leak sensitive information about their opponents. Genetic identity is not protected by the Canadian Human Rights Code, so genetic discrimination is legal.[15] Therefore, legislation similar to Bill S-201 or an amendment to the Canadian Human Rights Code would need to precede WGS in NBS to legally safeguard genetic identity.[12,15] Finally, it is important to question whether a facility housing the genetic identity of millions of Canadians could ever be secure enough to exist.

Another key question is the expansion of NBS programs to include disorders detectable by WGS.[11] Similarly to how tandem mass spectrometry rendered additional biochemical tests cheap after its initial cost, WGS would render testing costs for genetic disorders negligible beyond the cost of performing the sequencing.[11,12] This attribute means WGS would be most cost-effective if many new disorders were screened.[11,13] Although this seems intuitive, more factors than finance must be considered.[11] Expansion would worsen existing problems with unclear or false results, leading to unwarranted anxiety and follow-up testing.[3,6] Also, diseases screened in Canada are selected against stringent criteria; upholding these values mandates considerable time and work hours.[4-5,11] WGS would direct attention towards genetic disorders it could easily screen rather than ones benefiting the babies most. For example, Canadian NBS is insufficient in assessing hearing impairment.[13,14] Although a fix is underway, it is possible that disorders with non-genetic diagnostic methods, like hearing impairment, would be overshadowed in a post-WGS world.[13,14] WGS must be moulded to fit NBS, not the other way around.

Lastly, the introduction of WGS into NBS programs might encourage ethical compromises to achieve 'great' advancements. Consider the utility of being able to inform patients of high-penetrance variants of their increased susceptibility to atherosclerosis. They might adopt a healthier lifestyle, extending their lifespan and saving the government thousands in treatments and surgeries. Imagine the possibilities for genome-wide-association studies if 35 million Canadians were available as data points. Science and medicine would together advance in leaps and bounds. Such momentous projects may have a place in modern medicine, but not in the current NBS framework.[11] NBS is designed around children's health and is incompatible with expansion beyond this pure purpose.[11] We are much further from this scientifically and medically utopic future in our ethics than our technology. This is a gap we must bridge before seriously considering any such venture.

Some argue Canadian NBS programs should screen more disorders by modernizing technology to high-throughput techniques.[13] This makes WGS very attractive. It would enable the addition of novel disorders to NBS lists in an economical manner, albeit after substantial initial investment, and would also provide accurate diagnosis for all genetic disorders. WGS in NBS remains economically unviable, but a future with affordable WGS is approaching.[10,16] The costs or benefits of transitioning to genomic sequencing is irrelevant until the associated ethical conundrums are reconciled so that the integrity of NBS is maintained in the face of WGS. ■

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