Newborn screening (NBS) identifies treatable disorders in neonates through systematic testing. Upon diagnosis, prompt medical interventions can improve or manage the baby's health. 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.

The expansion of NBS in Canada has spurred initiatives to develop assays which screen for multiple disorders simultaneously. Despite this advancement, NBS remains sub-optimal, with high false-positive rates requiring cumbersome re-testing and follow-up. Furthermore, coverage of disorders in Canadian NBS is disjointed as each province or territory coordinates its own NBS program. 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.

WGS identifies all six-billion base pairs in the human genome, giving it the capacity to diagnose any genetic disorder. 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. This cost plummeted to just $4000 in mid-2015, and presently, the cost has dropped down to $1000. Many scientists predict that costs will continue to drop, making WGS in NBS feasible in the future.

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. Additionally, WGS gave fewer false-positives, resolved inconclusive results, identified causative mutations, and required fewer sample collections from preterm infants. In some cases, it even detected nuances distinguishing closely-related conditions indistinguishable by conventional NBS. 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. From this, an ethical quagmire arises that we are as-of-yet unprepared to face.

Disclosure of sequencing results represents one serious issue. NBS is designed to uncover actionable findings, whereas WGS would screen everything. 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 needless anxiety, and confirming results would be expensive and time-consuming.

Another important concern is data storage and usage. NBS samples are kept only short-term to avoid erasure 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.

Furthermore, there exist privacy concerns and the potential for abuse of sequencing results by third parties. 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. 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. Finally, it is important to question whether a facility housing the genetic identity of millions of Canadians could ever be safe enough to exist.

Another key question is the expansion of NBS programs to include disorders detectable by WGS. Similarly to how tandem mass spectrometry rendered additional biochemical tests cheap after its introduction, whole-genome sequencing for detection of newborn disorders in a population cohort of 1.796 million, Genetics in Medicine, 2015, 17(2), 121-127, suggests that WGS could be more cost-effective if many new disorders were screened. Although this seems intuitive, more factors than finance must be considered. Expansion would worsen existing problems with unclear or false results, leading to unwarranted anxiety and follow-up testing. Also, diseases screened in Canada are selected against stringent criteria; upholding these values mandates considerable time and work hours. 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. 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. 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. 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. 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. 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.