Managing sickle cell carrier results generated through newborn screening in Ontario: a precedent-setting policy story

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Forming public policy in the face of competing priorities is both an opportunity and a challenge for decision makers. The primary goal of newborn screening (NBS) is to identify babies with serious disorders for whom treatment is available before symptoms present.^{1,2} Newborn identification and early prophylactic antibiotic treatment of individuals with sickle cell disorders (SCDs) reduce the incidence of pneumococcal infections.³ Incidental to identifying individuals with SCDs, NBS also identifies most carriers of “sickle cell trait” (SCT). US screening programs routinely disclose these incidentally discovered carrier results to parents.⁴ However, when NBS in Ontario, Canada, expanded to include SCDs in 2006, a complex decision-making process ensued to define provincial policy regarding carrier disclosure. Ultimately, routine disclosure was *not* chosen as the policy; rather, disclosure of carrier status *upon parental request* was chosen. With the increasing use of next-generation sequencing techniques in NBS, the incidental discovery of carrier status and variants of uncertain or mild clinical significance will become increasingly common and raise new, and possibly different, policy challenges.^{5,6} The principles that underpinned the Ontario policy process regarding SCT disclosure may be highly instructive for future deliberations related to managing these results.

Although ascertainment of SCT is incidental to SCD screening, it has been argued that routine reporting of NBS-ascertained SCT status provides an opportunity to identify and counsel families about the parents’ and infants’ future reproductive risks.⁷ Others contend that generating this information for families is not a primary goal of NBS and that this is not a sensitive method of identifying all prospective parents or infants at risk.⁸ Other factors complicate the context. For example, professional guidelines recommend offering carrier screening to at-risk couples—for a host of medical conditions—during the reproductive years, while avoiding disclosure of carrier results

to children until they reach an age when they can understand the reproductive implications.⁹ In addition to providing reproductive-risk information, some substantiate disclosure based on the argument that SCT has health implications in high-performing athletes and that NBS provides a mechanism for equipping potential athletes with this knowledge.¹⁰ Although the National Collegiate Athletic Association policy cites risk of sudden death as justification for mandatory SCT screening for all Division I–III athletes, the American Academy of Pediatrics, the American Society of Hematology, the Secretary’s Advisory Committee on Heritable Disorders of Newborns and Children, and the Sickle Cell Disease Association of America contend that the connection between SCT and risk of sudden death has not been sufficiently established to warrant mandatory screening for collegiate athletic participation.¹⁰ These and related concerns will be germane when primary molecular approaches to NBS are implemented and incidental detection of carrier and other variants of uncertain/mild significance becomes routine.⁵

In Ontario, NBS is administered by Newborn Screening Ontario (NSO), which is based at the Children’s Hospital of Eastern Ontario in Ottawa. Of the 140,000 babies born annually, NSO identifies approximately 50 babies with SCDs and approximately 1,900 with SCT. On the advice of its Newborn and Childhood Screening Advisory Committee, the Ontario Government was reluctant to follow automatic disclosure policies that are in place in other jurisdictions.⁴ In addition to the issues noted here, government decision makers were concerned that routinely disclosed carrier results could be misunderstood or stigmatize individuals from an already marginalized community, could be costly, and might establish a troubling precedent regarding the routine identification and disclosure of incidental NBS findings. Instead, they commissioned an extensive stakeholder engagement to inform their response to this dilemma. Three key steps shaped Ontario’s response: (i) commissioned

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mixed-methods research, (ii) knowledge translation, and (iii) policy deliberation.

Commissioned research

The study included 1,615 health care–provider survey respondents and 122 interview/focus group participants comprising parents, health-care providers, and advocates. Three lines of peer-reviewed evidence warrant reflection.⁸ First, among survey respondents, the dominant view favored automatic disclosure. However, providers identified barriers to adequately educating parents about the possibility of SCT results prior to screening and counseling families with SCT results. Some opposed automatic disclosure, reasoning that the child should decide if/when he or she wants this information. Second, the pursuit of reproductive-risk information as an acceptable goal of NBS was contested; 74–77% of providers endorsed the identification of reproductive risks as a goal of NBS, but only half of the genetics professionals agreed. Third, respondents' interpretations of SCT were complex. Although participants generally believed that SCT was clinically insignificant, they equivocated about its significance on the basis of past knowledge, lived experience, or future possibility. Adding these mixed interpretations to an already complicated and racialized history of population screening for SCDs in North America (i.e., that served to the advantage and disadvantage of black individuals) posed challenges to creating clear educational messages about SCT identification in newborns.

Knowledge translation

Based on this research, the recommendation provided to the advisory committee was that *carrier status should be disclosed to parents, with an opt-out option*.⁸ The identification of disclosure as the dominant preference, coupled with important minority concerns, justified this recommendation. In turn, the advisory committee endorsed this recommendation, favoring a disclosure policy that enabled optionality and ensured appropriate education to mitigate potential misunderstanding of SCT results.

Policy development

A team at the Ontario Ministry of Health and Long-Term Care developed disclosure options based on this recommendation. Each policy option was considered against five criteria: alignment with evidence, alignment with other jurisdictions, degree of disclosure (i.e., active versus passive), degree of parental choice, and feasibility. Three primary options were considered: (i) automatic disclosure (i.e., parents automatically informed of results through NSO), (ii) opt-out disclosure (i.e., parents automatically informed of results unless they opt out), and (iii) opt-in disclosure (i.e., parents informed that results are available on request). After much deliberation with decision makers, the final policy direction specified that *SCT should be disclosed to parents with an option, and the implementation of this policy must be timely and executed within*

existing operational structures. These deliberations revealed that the criteria were not weighted equally; optionality and operational feasibility assumed priority whereas disclosure, alignment with commissioned research evidence, and alignment with other jurisdictions were secondary. Although an opt-out model of disclosure was supported by the research, this approach presented challenges related to timely mechanisms for opting out, ensuring privacy, and cost. Option iii—the opt-in disclosure model—was thus determined to be the best available solution and was implemented by NSO in November 2010.

Although the current approach does not optimize the opportunity for parents to learn about SCT risks through NBS,¹⁰ the Ontario policy community strongly believed that this was not a primary goal of such screening. Rather, as professional guidelines recommend, at-risk individuals are encouraged—of their own volition—to learn their carrier status during their reproductive years and to attend to strenuous exercise-induced risks in the same way that all competitive athletes are encouraged to do. Although NBS does provide one mechanism for this information—and needs to optimize its approach to ensuring that parents are aware of this option—it does not need to hold the sole responsibility of this broader educational goal. This is particularly the case when the educational message is complicated by current equivocation about whether SCT is truly benign or part of a “problem list.”¹⁰

The Ontario policy decision on reporting SCT generated through NBS was notable for its commitment to the primary goals of NBS, the importance placed on the resource implications of disclosing incidental findings, and development and use of jurisdiction-specific evidence to navigate competing policy interests and mitigate risks. The process and ultimate decision reflected the very real complexities of harmonizing evidence, competing interests and values, long-standing professional guidelines, and operational pressures. We are confident that the Ontario policy considered evidence in context and fairly balanced a multitude of competing interests. Implemented alongside an evaluative framework, an assessment of the strengths and limitations of this policy approach is under way to optimize its quality and gauge its generalizability to emerging NBS technologies.

Most importantly, the principles underpinning this process are vital to consider in deciding how to manage complex and analogous results that will be generated by next-generation sequencing-based NBS.⁵ CFTR (cystic fibrosis transmembrane conductance regulator) sequencing as a third-tier test for cystic fibrosis NBS, already implemented in California and under consideration in other jurisdictions, presents this precise challenge.⁶ In addition to carrier results, a broader spectrum of genotypic results associated with uncertain clinical significance or mild disease are being generated. Moreover, not all newborns currently receive CFTR sequencing, so these results will not be universally available. It is anticipated that targeted gene panel testing and broader next-generation sequencing-based technologies will be incorporated into screening

protocols; initially into reflexive second or third tiers but eventually into first-tier testing (i.e., applied to all newborns). This will not only increase the number of incidental variants discovered but also increase the complexity of incidental genotypes. Automatic disclosure is unlikely to be a viable strategy for managing this anticipated influx and complexity. Therefore, it will be essential to explicitly consider the fundamental principles delineated in the policy process in Ontario (i.e., optionality, education, operational feasibility) in policy decisions that confront the NBS community.

DISCLOSURE

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