Form 3. Template for a full review process for a condition being considered for addition to the newborn/child screening panel

****Note: please specify the basis for each answer and rely on published evidence (with cited references) whenever possible**

A. THE CONDITION

- ***The condition should be an important health problem.***
- ***The epidemiology and natural history of the condition should be adequately understood.***

Questions	**Responses, including basis for answers and references**
Case definition	
(1) Are there accepted diagnostic criteria? What are they?	
(2) Are there different variants? If so, can they be clearly distinguished?	
Condition frequency	
(3) What is the estimated prevalence of the condition in the target population?	
(4) Is prevalence known to vary across populations?	
(5) If applicable: has there been an increase in observed prevalence in jurisdictions with newborn or childhood screening for the condition?	
Natural history and severity	
(6) What are the characteristic clinical manifestations of the condition?	
(7) In the absence of screening, at what age do symptoms typically develop? What is the average age at diagnosis?	

(8) What is the spectrum of severity of the condition (mortality, morbidity, disability)?	
(9) Is there known clinical heterogeneity (e.g., in severity or timing of onset)? If so, are there known prognostic markers?	
(10) If applicable: how has the spectrum of severity of the condition changed in jurisdictions with newborn or childhood screening?	

B. THE TEST

- ***There should be a simple, safe, precise, and validated screening test.***
- ***The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.***
- ***The test should be acceptable to the population.***
- ***There should be an agreed policy on the further diagnostic investigation of individuals with a positive screening test result.***
- ***If the screening test includes a test for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.***

Questions	**Responses, including basis for answers and references**
Screening test modality and parameters	
(11) Is there a standard screening test? If so, what is the modality of the test (e.g., analysis of dried blood spots, bedside pulse oximetry, questionnaire-based assay)?	
(12) What is the proposed target population for the test (e.g., all newborns in Ontario)?	
(13) Is there any reason to be concerned about test acceptability in the population?	
(14) If the test modality is not analysis of dried blood spots and/or if the target population is not newborns, what is the proposed framework for test delivery (e.g., point of care, centralized analysis) and what are the system capacity considerations?	
(15) What analytes or parameters are included in the screening test (if there are multiple screening steps, answer separately for each step)?	
(16) Is the screening test part of a multiplex assay (e.g., tandem mass spectrometry)? If so, is this multiplex assay already being used to screen the same population in Ontario?	
(17) What ancillary information (e.g., about other conditions, carrier status) is generated by the screening test, if any?	
Analytic and clinical validity of the screening test (if the screening test has multiple steps, answer separately for each step where relevant)	
(18) Is the screening test qualitative or quantitative?	
(19) If the test is quantitative, is the distribution of values in a similar population known? Is there an agreed cut-off for a positive result?	

(20) Does the screening test include mutation testing? If so, is there an agreed set of mutations for testing (if so, specify rationale)?	
(21) Has the precision of the test been evaluated (based on repeated measures of same samples within or between laboratories)? What are the results of the evaluation of test precision?	
(22) Has the analytic accuracy of the test been evaluated? What are the results of this evaluation (e.g., validity based on standard or control samples, lower limit detection, linearity)?	
(23) Sensitivity: among those with the condition, what proportion is expected to receive a positive screening test result?	
(24) Specificity: among those without the condition, what proportion is expected receive a negative screening test result?	
(25) If applicable: what are the positive (and negative if known) predictive values of the test in similar populations (e.g., jurisdictions with screening where condition prevalence is expected to be similar to Ontario)?	
Diagnostic testing for those with positive screening test results	
(26) Is there an agreed strategy for diagnostic investigation of those with positive screening test results? What is the strategy (set of tests or investigations recommended)?	
(27) Does the diagnostic test or strategy clearly distinguish between those affected and not affected with the condition?	
(28) What is the proposed framework for delivery of diagnostic care (e.g., care delivered by specialist physicians at newborn screening treatment centres or tertiary care facilities) and what are the system capacity considerations?	
(29) What is the anticipated time between receipt of a positive screening test result by the diagnostic care system and reporting of the final diagnosis (for typical cases, and for the most challenging cases)?	
(30) Is there reason to be concerned about the acceptability of diagnostic investigations among families of screen-positive infants?	

C. THE TREATMENT

- ***There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.***
- ***There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.***
- ***Appropriate clinical management of the condition and patient outcomes should be available to newborns/children with the condition before population screening is initiated.***

Questions	**Responses, including basis for answers and references**
Description and availability	
(31) Are there established intervention/s for individuals diagnosed with the condition? What are these?	
(32) Are all individuals diagnosed with the condition candidates for the above-named intervention/s? If not, explain.	
(33) Do individuals with the condition in Ontario currently have access to these intervention/s? Are there concerns about access in terms of the costs of treatment and coverage of costs? Are there concerns about inequities in access to care in different patient groups? Are there system capacity issues to consider (and if so, what are these)?	
(34) Is there reason to be concerned about the acceptability of the intervention/s named above, either to families of screened infants/children or to health professionals who provide care?	
Effectiveness	
(35) Is there evidence from similar populations to support the effectiveness of the intervention/s in terms of **clinical benefits to affected individuals**? How strong is this evidence (e.g., randomized controlled trials, quasi-experimental studies, observational evidence)? References should be provided.	
(36) Is there evidence supporting the comparative effectiveness of intervention/s at an early stage of condition versus a later (symptomatic) stage of condition? How strong is this evidence? References should be provided.	

D. SOCIETAL CONSIDERATIONS

- ***There should be evidence that the screening program is effective in reducing mortality or morbidity.***
- ***There should be evidence that the complete screening program (tests, diagnostic procedures, treatments/interventions) is clinically, socially, and ethically acceptable to health professionals and to the public.***
- ***The benefit from the screening program should outweigh the physical and psychological harm (caused by the test, diagnostic procedures, and treatment).***
- ***The opportunity cost of the screening program (including testing, diagnosis, treatment, administration, training, and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole.***

Questions	**Responses, including references**
Overall benefits and acceptability	
(37) Is there evidence to support the overall benefit of screening for this condition in newborns/children (e.g., based on evaluations in other jurisdictions), in terms of clinical benefits to individuals with the screened condition? How strong is this evidence?	
(38) What are the other potential benefits of screening for this condition in newborns/children, for screened children, their families, or society (e.g., avoidance of diagnostic delay; an information benefit to parents in terms of reproductive risk for inherited condition; opportunity to better understand the natural history of condition and study the benefit of early intervention; incidental identification of non-targeted conditions that would benefit from intervention)? Is there evidence to support these benefits?	
(39) Is there evidence to support the acceptability of screening for this condition in newborns/children, among families of screened children, the public, and/or health professionals?	
Potential harms	
(40) Is screening for this condition expected to lead to overdiagnosis (identification of very mild or asymptomatic cases that would be unlikely to come to clinical attention/cause harm in the absence of screening)? If so, what is the likely extent of overdiagnosis? What harms (including psychosocial harms) are anticipated? Is there evidence regarding the degree of harm from overdiagnosis?	

(41) What is the anticipated false positive rate (1-specificity)? What harms are anticipated due to false positive screening results in this case? Is there evidence regarding the degree of harm (including psychosocial harm) from false positive results?	
(42) Is screening for this condition in newborns/children likely to lead to the incidental identification of health conditions that are not targets of screening? If so, what harms are anticipated (if any) due to this incidental identification (physical and/or psychosocial)? Is there evidence regarding the degree of expected harm?	
(43) Is screening for this condition in newborns/children likely to lead to the incidental identification of non-affected heterozygous mutation carriers for the condition? If so, what related harms are anticipated (if any) (including psychosocial harms)? What is the proposed policy for disclosure of carrier status?	
(44) Are any other potential harms anticipated from the screening test, diagnostic care, treatment, or other aspects of screening?	
Resource needs and cost-effectiveness	
(45) What additional resources (for screening, diagnosis, treatment, genetic counseling, education, etc) are likely to be needed to support screening for this condition among Ontario newborns/children (qualitatively: it is not necessary to estimate actual monetary costs)?	
(46) Is there published evidence to support the cost-effectiveness of screening for this condition in a similar population?	
Other considerations	
(47) If the proposed addition is other than an addition to the existing newborn blood spot screening program, what model of parental consent is proposed?	
(48) Are there any unique privacy considerations or other ethical considerations associated with the proposed screening (aside from existing considerations for Ontario's newborn blood spot screening program)? If so, please explain (e.g., relevant to the collection and use of personal health information or samples)?	

E. SUMMARY AND SUB-COMMITTEE RECOMMENDATION
***Section E should be left blank by the reviewers. It will be completed by the sub-committee through discussion of the review.**

Conclusions by section:

The condition (Section A)
☐ No concerns
☐ Some concerns or some uncertainty about this section
☐ Concerns in this section of the evaluation are serious enough to warrant recommending against screening at this time

Comment:

The test (Section B)
☐ No concerns
☐ Some concerns or some uncertainty about this section
☐ Concerns in this section of the evaluation are serious enough to warrant recommending against screening at this time

Comment:

The treatment (Section C)
☐ No concerns
☐ Some concerns or some uncertainty about this section
☐ Concerns in this section of the evaluation are serious enough to warrant recommending against screening at this time

Comment:

Societal considerations (Section D)
☐ No concerns
☐ Some concerns or some uncertainty about this section
☐ Concerns in this section of the evaluation are serious enough to warrant recommending against screening at this time

Final conclusion and rationale, considering all sections together:

REFERENCES